AERO-OTITIS MEDIA AND AEROSINUSITIS

EXPERIMENTAL HISTO-PATHOLOGICAL CHANGES DUE TO OXYGEN DEFICIENCY AND OXYGEN POISONING

By

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UPPSALA 1948

FROM THE HISTOLOGICAL DEPARTMENT (HEAD: PROFESSOR MARTIN WRETE) AND THE OTO-RHINO-LARYNGOLOGICAL CLINIC OF THE ACADEMIC HOSPITAL (HEAD: PROFESSOR C. O. NYLÉN) OF THE UNIVERSITY OF UPPSALA, SWEDEN.

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776/39

TRANSLATED

BY

ULLA SCHÖTT

Also in

ACTA OTO-LARYNGOLOGICA

(Supplementum LXIX)

UPPSALA 1948

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I.

Preface

During the second world war I had the privilege of serving, for part of the time, at the Royal Swedish Air Force. Thanks, not least, to the kindness of my medical superiors, I was there placed in a position to study the medical aspects of aviation, theoretically and practically. Through experiences thus gained my attention was gradually drawn to the problems which form the subject of this investigation.

The studies were initiated in 1944 at the Oto-rhino-laryngological Department at Uppsala. I have much pleasure in recording here my deep gratitude to Professor Carl Olof Nylén, Head of that Department, for the kind interest he has taken in my work and for valuable discussions regarding the clinical aspects of various questions. I am particularly obliged to Professor Nylén for allowing me to combine my duties at his Clinic with these investigations.

At an early stage it became obvious that the task I had undertaken would require more extensive resources than the Otological Clinic can offer at present. Professor Martin Wrete, Head of the Histological Department of Uppsala University, then most generously extended to me the facilities of his Institution. During a period of more than three years I have enjoyed the pleasant working conditions of Professor Wrete's Department. I am glad to express here my warmest thanks to him for all his personal encouragement and ureful criticism.

I am greatly indebted to Professor Nils Gellerstedt of the Pathological Department of Uppsala University for his expert assistance in judging various histological preparations.

My thanks are also due to Professor Torsten Teorell, Head of the Physiological Department of Uppsala University, and to Mr Henrik Enghoff, M. D., Laborator of the same Depart-

ment, for many interesting discussions and suggestions, and to the latter also for his courtesy in lending me the apparatus required for the gas analyses.

I am also most grateful to Docent HILDING BJURSTEDT, M. D., Stockholm, for excellent advice and help, particularly concerning the physiological problems I have had to solve in the course of the inquiries, and also with regard to the presentation of my investigations.

To the Chief Assistant of the State Institute of Human Genetics and Race Biology, Mr ELVIR LANDER, I am extremely obliged for the help he has rendered in connection with the statistical calculations.

I also wish to put on record my deep appreciation of Professor AXEL LINDH's kindness in permitting me to build the apparatus needed for the investigations within the precincts of the Institute of Physics of Uppsala University, and to thank, at the same time, most warmly, Mr JOHN AMBERNTSSON, the Instrument Manufacturer, for the care and attention he devoted to the construction of that apparatus.

Finally, I am very pleased to express my sincere obligation to the staff of the Histological Department, Mr AXEL HALVARDSON, Miss BERTA SANDÉN, Mrs INGA-BRITT RYDE, Miss KERSTIN JANSSON, Miss KARIN BARKANDER and Mr THORE WAHLUND. Mr Halvardson has been good enough to assist me in the taking of the photos. Most of the histological preparations have been made by Mrs Ryde and Miss Jansson.

Financial support for the investigation has been given by the State Committee for Aviation Medicine, by the Regnell Foundation of the Medical Faculty of University of Uppsala and from a State grant for the promotion of medical research.

Uppsala in December 1947.

Gunnar Aschan.

II.

Introduction and history

In his work "La Pression Barométrique", published in 1878, Paul Bert, the French scientist, gives a fascinating account of the first medical experiences from various flights. Records of ear troubles in connection with balloon ascents are to be found as early as in 1783 when Pilâtre de Rozier, in a balloon constructed by Montgolfier, reached a height of 3000 m (9140 feet). In 1862, Glashier and Coxwell attained an altitude of 7100 m (18590 feet). Glashier stated that after his descent he felt troubled by pains in his ears, a sense of aural occlusion and a slight deafness.

Gradually the two clinical conceptions of aero-otitis media and aerosinusitis have come to designate such symptoms in the form of congestion, inflammation, discomfort and pain in the middle ear and over the accessory sinuses, as will occur in connection with aviation. During the first world war, but to a much greater extent during the second world war with its tremendous development in aviation often at extremely high altitudes, these affections played a considerable part and, as a matter of course, they still attract a great deal of attention.

Below a compilation will be given of clinical observations regarding aero-otitis media and aerosinusitis in aviation and low pressure chamber tests, as well as of partly similar studies concerning compressed air workers, where the same clinical terminology has been in use. The experimental observations on the same subjects will be dealt with separately.

Clinical observations regarding aero-otitis media in aviation and in low pressure chamber flights.

Such novel human sensations and experiences as are connected with life at high altitudes very early attracted the attention of physiologists. Aero-medical research can, however, only be said

to date from the first world war. To this study the oto-rhinologists have contributed from the outset. By otoscopy of aviators after flying, Lacroix (1917) noted changes in the tympanic membrane in the form of an injection along the malleus handle and an "intense congestion" of Shrapnell's membrane. Marchoux and Nepper (1919) performed experiments in Paul Bert's low pressure chamber. Several of the test persons suffered from intense pains in their ears and over the sinuses. Their experiences were summed up as follows: "Any obstruction which prevents the rapid establishment of pressure equilibrium between the cranial spaces and the outside atmosphere involves the possibility of a series of misfortunes in which pain is one of the least and syncope one of the most serious." In several instances Scott (1919—20) noticed changes in the tympanic membrane in aviators concluding with a warning against flying with a cold in the head.

In 1937 Armstrong and Heim published a paper on "The effect of flight on the middle ear". It has been accepted as a fundamental work on this subject. They introduced the conception of *aero-otitis media* with the following definition: "Aero-otitis media is an acute or chronic traumatic inflammation of the middle ear caused by a pressure difference between the air in the tympanic cavity and that of the surrounding atmosphere, commonly occurring during changes in altitude in aeroplane flights and characterized by inflammation, discomfort, pain, tinnitus and deafness." The essential element in the process should thus consist in a lack of pressure equilibrium through the failure of the pharyngotympanic tube to follow the rapid changes of pressure during a descent. Patho-anatomically they define the process as a traumatic inflammation with a hyperemia in the mucous membrane of the tympanic cavity. They base their conclusions exclusively on clinical experiences of flights or on low pressure chamber tests. As a matter of course, histo-pathological observations are lacking, nor have they performed any animal tests.

In the figure presented below Frenzel (1939) has produced a schematic illustration of the same idea.

The second world war with its immense aero-technical progress, quantitatively as well as qualitatively, brought new experiences

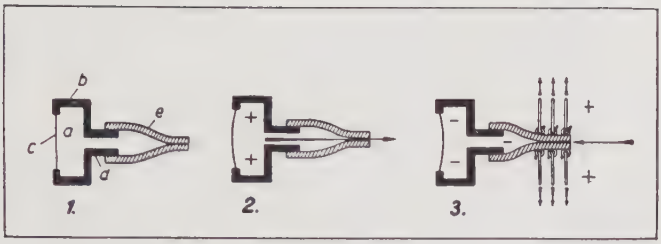

Fig. 1. Schematic figure showing the pressures in the tympanic cavity and the function of the tube during decompression and recompression (after Frenzel). a = the middle ear, b = the bone capsula of the tympanic cavity, c = the tympanic membrane, d = the bone part and e = the cartilaginous part of the pharyngotympanic tube which normally is closed. 1. denotes normal condition, 2. the decompression, when the air is pressed out of the middle ear, 3. shows the recompression. The air cannot pass into the middle ear, unless the muscular power, i.e. tensor veli palatini, separates the walls of the tube, which acts as a valve. At pressure differences of 80—90 mm Hg or more such an opening of the valve cannot take place.

also in this field. However, without exception the authors who have studied the aero-otitis media, in explaining its genesis, altogether depend on Armstrong and Heim. In the abundant literature on the subject the authors offer but general statements unaccompanied by any material of their own. Such statements will be entirely ignored here. That aero-otitis media has constituted a serious medical problem is obvious from the wide publicity it has caused. Nevertheless, available morbidity figures present a considerably more striking picture of the situation. Wright (1944) found that 6 per cent of "100 000 men who made routine flights in the low pressure chamber developed aero-otitis media". Lieberman (1946) records a morbidity of 16.6 per cent in low pressure chamber flights, while an additional 27.9 per cent showed otoscopic changes in the tympanic membrane without such subjective troubles as were ascribed to the diagnosis of aero-otitis. Stewart et al. (1945) arrived at a morbidity of 13 per cent, while 50 per cent of the test persons showed otoscopic changes in the tympanic membrane. It may be noted, in passing, that they adopt the term of *otitic barotrauma* as synonymous with aero-otitis media, as is usual in English literature. Also the term *aviation pressure deafness* (McGibbon, 1941) is used as a synonym for aero-otitis media.

Dickson et al. (1944) tested 1000 aviation cadets in low pressure

chamber flights with ascents up to 10 000 feet (3050 m). 89 developed aero-otitis media, while a further 325 disclosed a varying degree of hyperemia in the tympanic membrane, among whom 48 with faint or rapidly disappearing subjective troubles. All these particulars accentuate the importance of counteracting measures. That 6—16 per cent of the airmen remain on the sick-list, sometimes for periods up to four weeks, is a matter not to be disregarded from the point of view of training and fighting efficiency.

Scott's previously quoted statement, "a pilot shouldn't fly with a cold in his head", returns throughout all the literature mentioned above. A not inconsiderable etiological significance is attributed to upper respiratory infections. Still, it is but rarely that an analysis is offered in support of this contention, and the conclusion arrived at by the present writer has often been that no such connection has proved definitely ascertainable. McGibbon (1941) is alone in noting a comparatively high percentage of infections. Among 100 cases of aero-otitis media in his material one third showed inflammations of the nasopharynx, or adenoid vegetation, septum anomalies, chronic tonsillitis or sinusitis. Yet, only 6 of these cases have been classified as acute colds. In Wright's latest paper (1945), comprising 150 000 low pressure chamber flights, the morbidity in aero-otitis media amounts to 6 per cent. Only 39 of these 9000 cases were complicated with suppurative otitis. To Dysart (1946) this low frequency of infection is a surprise. He states: "Why so little acute suppurative otitis media has developed has been an unsolved problem." In his material of 100 cases of aero-otitis media Lentine (1946) could ascertain signs of rhinopharyngitis only in 7 per cent. He noticed no suppurative otitis.

More successfully than probably any other authors Stewart et al. (1945) have tried to analyse the problem of aero-otitis media, from the point of view of infection. Series of comparisons between low pressure chamber flights of persons with and without infections in the upper air passages produced no significant difference.

In this graphic description the morbidity of infections of the upper air passages, as well as of aero-otitis media (otitic

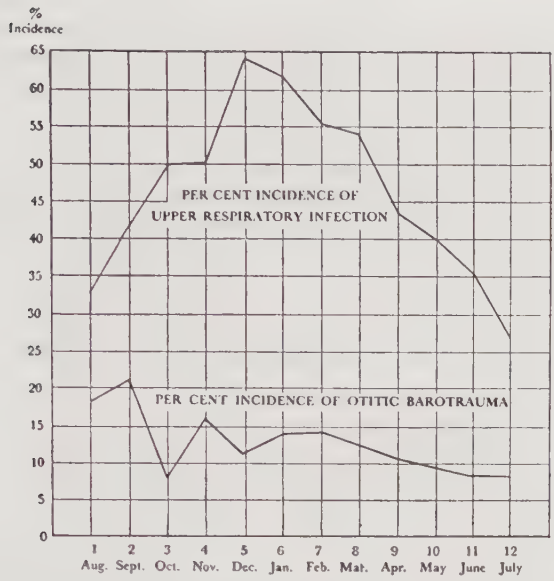

Fig. 2. The connection between upper respiratory infections and otitic barotrauma (aero-otitis media) acc. STEWART et al. (1945).

barotrauma), has been specified from month to month. As will be seen, no connection exists between the two. The authors summarize their experiences as follows: "Over-emphasis on the danger of a head cold has caused undue apprehension among airmen." ARMSTRONG (1943) has published a diagram similar to the one of STEWART et al., quoted above, suggesting a rough correlation between the incidence of upper respiratory infections and aero-otitis media. His investigations, however, cover but a period of three months, nor does he state the size of his material. The material of STEWART et al. is well analysed, comprising a group of 14 989 airmen, covering one year, as shown in the diagram (Fig. 2).

Should the rapid recompression at a descent possess such etiological significance as has been attributed to it, strongly pronounced changes ought to be noted in airmen after parachute jumps, when they fall freely from high altitudes and only open the parachute when approaching the ground. In 1938 James Nilaud, alias Williams, an experienced parachute jumper, per-

formed several jumps, the highest one with a free fall from 11 000 m in 170 seconds, without suffering any subjective ear troubles. Next day a slight injection of the tympanic membrane was noticed in him without any reduced hearing or any subjective troubles (Bergeret 1939). Apart from the forementioned data I have been unable to find any information in the literature concerning parachute jumps and their medical effects with special regard to the problem from this point of view.

Clinical observations regarding aero-otitis media in compressed air workers.

Aero-otitis media is often used as a clinical diagnosis in the case of aural symptoms in compressed air workers, such as divers, tunnel workers etc. According to Behnke and Willmon (1941) these symptoms were described as early as in 1900 by Heller, Mager, and von Schrötter. Like Behnke and Willmon (1941), Requart (1941) considered the differences in pressure between the middle ear and the surrounding atmosphere as an essential cause. Compared to aero-otitis media in airmen, the position is here the same, in so far as the difficulties in pressure equalization will appear at compression (cp. Frenzel's schematic picture fig. 1). Thus the parallelism with the previously cited analysis by Armstrong and Heim (1937) is complete. The increase in pressure at the descent would be so rapid as to cause the pharyngotympanic tube to act as a valve, rendering the passage of the air up into the middle ear difficult or impossible.

Clinical observations regarding aerosinusitis.

The first observation of troubles from the nasal accessory sinuses will be found in the forementioned article by Marchoux and Nepper (1919). Brouwer (1935) regarded sinusitis as a professional disease in airmen. In 1941 Herrmann described a case of submucous hematoma in a dive bomber pilot.

Pastore (1941) mentions pains over the sinuses in pilots, caused by mucosal hemorrhages or acute sinusitis — "not a rare clinical picture among aviators", he states. Campbell (1942, 1944, 1945)

has devoted much attention to the elucidation of these particular problems and in a series of papers he has dealt with the genesis, as well as with the clinical and therapeutical treatment. In analogy with ARMSTRONG's conception of aero-otitis media, he defines *aerosinusitis* as follows: "Aerosinusitis is an acute or chronic inflammation of one or more of the nasal accessory sinuses produced by a barometric pressure difference between the air or gas inside the sinuses and that of the surrounding atmosphere. It is commonly characterized by congestion and inflammation of the lining structures. Pain over the area of the sinuses is usually present. Mucosal or submucosal hemorrhage may occur." Two factors are supposed to render gas pressure equalization difficult, viz., the presence of fluid, mucous, pus or something similar, or an obstruction formed by hypertrophic tissue or anatomical deformities. Analogously, CAMPBELL differentiates between non-obstructive and obstructive aerosinusitis. He, as well as WRIGHT and BOYD (1945), mention a morbidity of 1—1.9 per cent. They also state that the presence of a nasopharyngitis or a deviated septum does not seem to be as great a determining factor in the production of aerosinusitis as is generally supposed, but they admit that in some cases resection of the septum was effective in preventing further trouble.

The term *aero-hematoma* of the sinuses was introduced in 1946 by WRIGHT and BOYD when relating 12 cases similar to that previously referred to by HERRMANN. 11 of these fell ill after low pressure chamber flights. DICKINSON and VOELKER (1945) described a similar case.

Pathological and experimental investigations.

Contrary to the clinical data regarding aero-otitis media and aerosinusitis, pathological examinations and animal tests are exceedingly sparse.

As far as the middle ear is concerned, patho-anatomical examinations of Man are entirely lacking. With regard to aerosinusitis available data are limited to the aero-hematomas described by HERRMANN (1941) and WRIGHT and BOYD (1945), two of which were operated and patho-anatomically verified.

Bergeret and Giorand (1939 a) exposed rabbits, dogs, monkeys, etc., to explosive decompressions up to altitudes corresponding to 5 000—13 000 m, with subsequent recompression for 4 minutes to ordinary atmospheric pressure. In 19 out of 21 cases a bleeding, usually in the shape of a hanging drop, was observed in the middle ear. In no instance was the tympanic membrane ruptured. No microscopical investigations were performed. The experiments were arranged in such a way as hardly to suggest any similarity with such "barotraumas" as happen to aviators. The experimental investigations are far from being immune from criticism. For instance, Bergeret and Giorand might as well have obtained their ear findings from the following recompression from 13 000 m as from the decompression. The decompression has in many cases taken place so rapidly that in several instances the possibility of gas-emboli, causing vascular disturbances, cannot be excluded.

Vail (1929) performed experiments on rabbits and dogs under high pressure, noting changes in the middle ear, mostly characterized by a copious hemorrhage. However, his experiments invite criticism, considering the fact that he closed the pharyngotympanic tube experimentally and, further, that owing to the rapidity of the decompression the possibility of air-emboli cannot be eliminated. Rips (1939) performed his compression experiments as follows: He first subjected animals to a pressure of 4 atmospheres, then performed a sudden or gradual recompression. In the former instance he obtained air-emboli and intense hemorrhages in the middle and inner ear. In the latter case, when the animals, during a period of 4—6 weeks, were daily exposed to a pressure of 4 atmospheres, followed by gradual decompressions, he noticed histological changes chiefly in the middle ear, consisting of edemas and extravasation of blood in the mucous membrane of the middle ear, and also, though but rarely, minor changes in the inner ear. These experiments will be referred to later. They cannot be accepted as unambiguous, seeing that Rips has employed the device of partly closing the nostrils of the test animals.

Gurkow (1940) performed low pressure chamber tests on 69 animals. With varying ascent and descent velocities they were

exposed to pressures corresponding to altitudes of 13 000 m. He noticed in these cases a hyperemia in the sinusal mucous membranes with expanded lympho-spatia and edemas, and mucosal hemorrhages to varying extents, now and then in the form of hematomas detaching the mucous membrane from the wall of the bone. Later, continuing his experiments with test animals, he measured the intrasinusal pressure after flights in a low pressure chamber finding a lowered pressure of 5—30 cm H_2O, which could be maintained for up to 40 minutes, i.e. an exceedingly moderate low pressure which can hardly explain the extensive changes which he mentions, nor corresponds to such reductions in pressure of 400—600 mm Hg to which the test animals were subjected. For various reasons a critical attitude to his conclusions is justified even though the changes in the mucous membranes which he describes remain of an obvious interest. Gurkow quotes an investigation by Magnotti which I have been unable to trace in available literature. Also Campbell (1945) has carried out experimental tests, though on only one single dog. Obstruction of the sinus ostium in the low pressure chamber and later recompression to sea level caused subserous hemorrhages.

III.

The Problem

Aero-otitis media and aerosinusitis are well established and defined clinical conceptions, but their pathological anatomy and patho-genesis cannot be said to be entirely explained. The generally accepted view of the genesis of Armstrong and Heim (1937), implying that, at recompression, the tube is not allowed the time required for restoring the pressure in the middle ear and the sinuses, respectively, at the same rate as the pressure increases, leaves several questions unanswered. Why are uniform clinical pictures caused by both an increase and a decrease of the ambient pressure? Why do otoscopic changes without any subjective troubles appear in such a preponderant number of cases as against clinical aero-otitis media? Supposing a rhinopharyngitis with troublesome tubal passage to be essential, why should these patients not already suffer from an otosalpingitis, and why is the risk of complication with suppurative otitis small to the point of non-existence? If a patient with an acute aero-otitis media is subjected to immediate treatment and the pressure equalized by politzerization or some similar method, why should, nevertheless, a morbid condition, lasting sometimes up to 4 weeks, occur?

All these questions seem to call for an attempt to ascertain whether any other factors than the tube function, as previously supposed, can play a part with regard to the origin of aero-otitis media and aerosinusitis.

As will be seen from the literature reported in the general discussion, clinical and experimental facts speak in favour of the assumption that the oxygen partial pressure, e.g., concerning oxygen poisoning, would cause symptoms and changes in the mucosal membranes of the upper respiratory tract as well as in the lungs. For this reason, the tests have been carried out at

different oxygen pressures produced both by reduction in low pressure chamber and by changed oxygen volume percentage in the air. The investigation was extended to include morphological studies of the lungs, firstly because, for instance, oxygen poisoning in human subjects will give symptoms from the middle ear and the nose as well as the lungs, secondly since, judging from the literature, pulmonary changes reported from oxygen deficiency and oxygen poisoning can be rather uniform.

The first tests were carried out on albino rats but, for several reasons rabbits were used for the conclusive experiments.

For want of clinical material of a sufficient size the present investigation has necessarily had to be limited to animal tests.

IV.

Experiments on albino rats

The anatomy of the middle ear and the upper respiratory tract of the albino rat.

The tympanic cavity is well developed in the albino rat. It is characterized by a large bulla ossea with an extensive wide lumen in the anterior part of the middle ear; backwards the space narrows. In the postero-lateral wall the tympanic membrane is framed into a ring-shaped crista opening upwards. The auditory ossicles are somewhat raised in the moderately developed epitympanic recess. The whole middle ear is covered by a thin mucous membrane, the lamina propria of which is overlaid with a uni- or bi-stratified low epithelium without cilia. Only around the tubal orifice itself the epithelium may assume the shape of a cubical or cylindrical ciliated epithelium. The pharyngotympanic tube opens into the antero-medial wall. Its length equals 1—1.5 mm only. In a transverse section it discloses a semi-oval lumen covered with a ciliated cylindrical epithelium with a profusion of goblet cells. The tubal cartilage takes the shape of a slightly bent plate partly comprising the upper and medial part of the tubal mucous membrane. As indicated in the anatomical pictures (fig. 20), the tube of a rat is permanently open which can easily be proved by low pressure tests. Changes in pressure do not affect the tympanic membrane. Pressure equalization is immediate.

In broad outlines the anatomy will appear from the appended semi-schematic picture. Some measurements illustrating the approximate order of magnitude may be worth noting. The maximum length from the anterior part backwards is about 3—4 mm, the maximum breadth, on a level with the tubal inlet, 2.8—3 mm, the height, at the last—mentioned level, 3—4 mm, the breadth

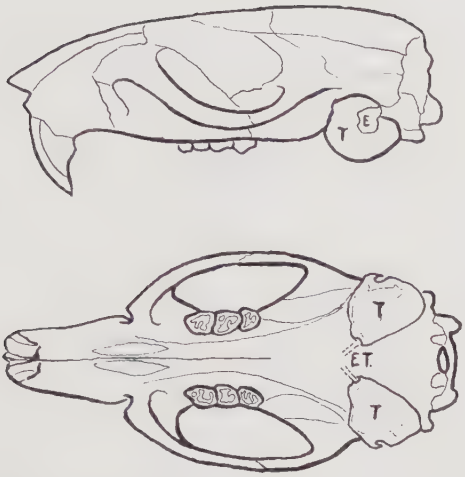

Fig. 3. Semi-schematic figure of skull of rat, viewed laterally and ventrally. T denotes the well developed bulla ossea, E the defect in the bulla by the external acoustic canal and ET schematic extent of pharyngotympanic tube. In the picture below, the middle ear has been marked by dotted lines.

tympanic membrane-promontory 0.8—1 mm. Considerable individual variations occur. Owing to the pronounced development of the conchae, the nasal passages of the white rat partly follow a very complicated course. On the other hand, the paranasal sinuses are badly developed, appearing in a transverse section through the nose merely as a fissure-like lumen.

Material and methods.

As early as in 1878 Paul Bert adopted a low pressure chamber for the purpose of studying the physiological effect of changes in the atmospheric pressure. Since then this has become the usual method in aero-medical research. Its advantages, as against experiments performed during actual flights, are too obvious to render any further remarks necessary. It will suffice to indicate the possibilities that offer themselves by this procedure to examine the various factors that make up the conception of a "barotrauma".

For the purpose of the present investigation a modest low pressure chamber had to be built, suitable for such test animals,

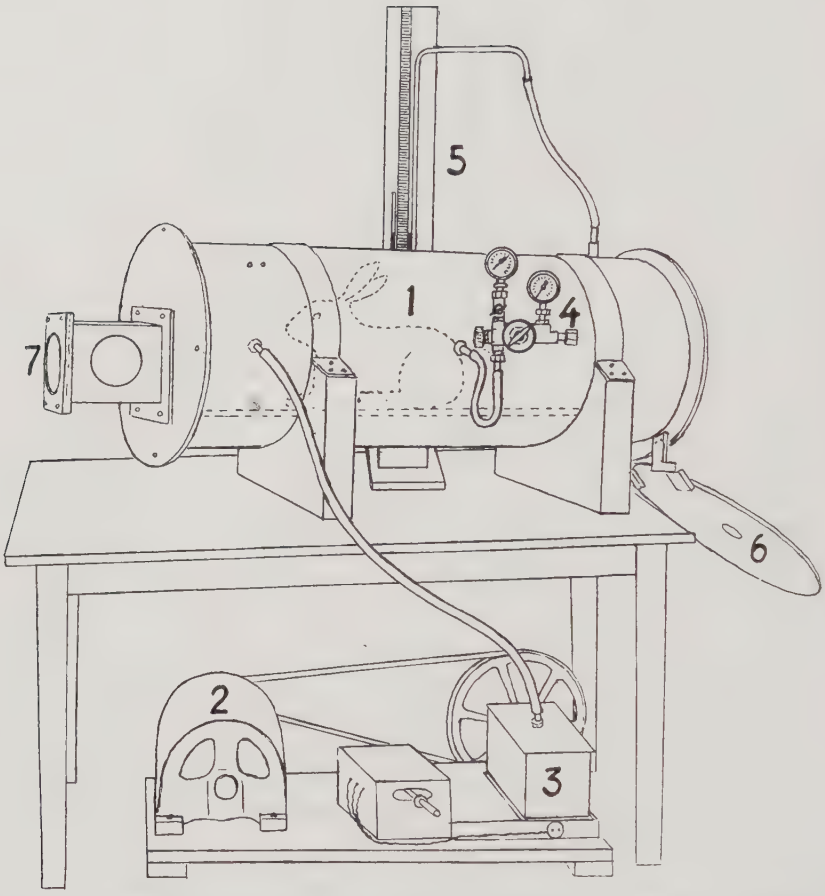

Fig. 4. Schematic figure of the low pressure apparatus 1. Chamber. 2. Motor. 3. Evacuation pump (oil-). 4. Reduction valve regulating gas inflow. 5. Manometer, open mercury manometer. 6. Door to chamber with small observation window. 7. Added structure, with observation windows, into which the head of the animal can be inserted by means of sliding operation-table.

white rats and rabbits, as were to be used. Because of the wartime shortages of material regard had to some extent to be paid to what was or was not at disposal, e.g., in the matter of evacuation-pumps, etc.

The low pressure chamber consists of a tube of steel of a centimetre's thickness. The tube is closed at both ends by plane-ground steel plates with a rubber packing against flanges welded

to the tube. One of the plates serves as a door and is provided with an observation window. To the other plate has been added a cubical structure with observation windows for the purpose of studying, with or without magnification, e.g., the movements of the tympanic membrane during low pressure experiments. By a number of small openings in the wall the evacuation-pump, gauge and gas inlet have been affixed. Reduction in pressure has mostly been effected by an oil pump capable of producing a reduction of 400 mm/Hg in 3—4 minutes. By regulating air or gas inflow into the chamber, by means of a reduction valve of the usual type, a desired pressure has been kept constant within the chamber while, at the same time, air conditioning has been efficient enough to preclude the likelihood of any considerable increase in the CO_2 pressure in the evacuated air or gas mixture. The chamber has a holding capacity of 51 litres. At 1 atmosphere the suction capacity of the pump is about 100 l/min. At a pressure reduction in the chamber of 400 mm/Hg and full suction power 30—40 l/min. must flow into the chamber in order to keep the stipulated pressure at a constant level. The pressure was measured by means of an open Hg-manometer, coupled to the chamber, the free surfaces of the Hg-column being covered with a drop of oil.

The rats were selected partly from the Histological Institution's own breed, partly from an animal farm. For the purpose of the experiments animals of an age of 4—5 months of both sexes were chosen. Already at an early stage all animals from the Histological Institution revealed signs of infections in the nasal sinuses, mostly in the form of dried secretions below the nostrils. The animals gave audible signs of difficulties in clearing the nasal passages, trying to expel the obstruction in their nostrils with a sneeze-like sound. These troubles affected all the animals both in tests and controls. For this reason the first experiments were discontinued and all the animals (more than 120) were killed. A new set of animals was obtained. None of these disclosed any of the forementioned signs of infection. Also otherwise they appeared healthy and vigorous, with a fine-looking fur, no nodules below the nostrils, no epithelial changes in the tail or the external ear.

In the final experiments on rats 93 animals were concerned. 40 were set apart as controls. The others were divided into two series. For an hour twice a day during a fortnight all the animals were subjected to a reduction in pressure of 400 mm Hg. However, during the reduction in pressure oxygen was substituted for air in one of the series of animals, while those of the other series were given ordinary indoor air.

Immediately after the last flight all animals were killed by decapitation after a light intraperitoneal numal narcosis. In order to obtain better fixation, the skull cavity was opened and the brain removed. The fixation was then carried out in a 10 per cent formalin solution. After decalcification in 5 per cent nitrous acid all superfluous parts of the head were extracted, such as the lower jaw. By means of two frontal incisions the paranasal sinus and the nasal sinuses were removed in one piece, the posterior part of the skull with tubas and ears was cut off by another frontal incision immediately in front of the tubal orifice. These pieces were in the usual manner embedded in paraffin. From the nasal sample a frontal test incision was made, while the ear-tuba-preparation was subjected to serial sectioning in frontal incisions of a thickness of 10 μ, every tenth section being exposed. Staining was performed with hematoxylin-eosine. The control animals were treated in the same way.

Microscopic examination disclosed variously pronounced inflammatory changes in the nose, the paranasal sinuses and in the middle ear of all the animals, including the controls, notwithstanding the fact that macroscopically they had been found "healthy" (Fig. 16—19).

In order to obtain a statistical record of the results, an attempt had to be made to register the degree of inflammatory irritation. On a section through the tympanic orifice of the tube the thickness of the mucous membrane of the middle ear, superiorly and inferiorly, was measured, by means of an ocular micrometer. These two values were added together. Further, the thickness of the tympanic membrane of the same section was measured. The measurements of the different sections were, as far as possible, taken at corresponding points in the sections. The procedure adopted for obtaining the measurements will appear from Figs.

17, 18. The measured distances are represented by black lines from the epithelium passing towards the tympanic cavity to the endo-ostium on the inner side of bulla ossea. The same optics and ocular micrometer were employed in all measurements. One unit of measure corresponds to 19.2 μ. There has been no need to check the values over again, seeing that only quantitative comparisons have mattered. In order further to elucidate the degree of inflammation the occurrence of exudation on the measured section, as well as behind Shrapnell's membrane, has been noted. From the amount of exudation, and, to some extent, from its content of cells, three groups have been distinguished, group I indicating little or no exudate, II a moderate amount, and III a profuse amount.

For the statistical analysis current methods have been applied (Dahlberg, 1940). Mention need only be made of the fact that the difference between two means or percentages is accepted as statistically significant when amounting to at least 3 times the standard error of the difference.

The method error in measuring the thickness of the mucous membrane and the tympanic membrane has been calculated on the basis of 54 double determinations. The method error of σ_m has been obtained according to the following formula:

$$\sigma_m = \sqrt{\frac{\Sigma d^2}{2n}}$$

Σd^2 denotes the sum of the squares of the differences between the two determinations.

At an average thickness of 42, the value of σ_m equals 3.3 or 7.8 per cent of the mean. With lower values of thickness the method error is relatively somewhat bigger. At a thickness of 5.4 σ_m equals 0.67 or 12.5 per cent. In measuring the thickness of the tympanic membrane the method error is of the same order of magnitude. The obtained value of σ_m implies that the "true" measure of the thickness of the observed tissue will with a probability of 0.68 differ at most 8—13 per cent from the observed measure. The probability is equivalent to 0.95 that the "true" measure will deviate less than 15—25 per cent from the observed one. Thus, the method error is of moderate size. In this con-

nection it should, however, be emphasized that the method error has significance only for the estimation of the accuracy of an individual determination. The means, recorded in the tables below, are affected but very slightly by the method error.

With regard to the character of the exudation, the material has been divided into the three forementioned groups according to the appearance of the exudate. It is of interest to ascertain the degree of accuracy of this classification. For this purpose 54 individuals were on two different occasions separated into their three different groups. The results conformed well in both instances, 83.3 per cent, were found in the same group on both occasions. The deviations in the opposite directions partly neutralize each other. As already stated, the final result of the division into three groups fairly conforms from one occasion to the other. The accuracy of the classification can thus be regarded as satisfactory.

The result of the investigation.

Mean figures with their mean errors have been computed for the thickness of the mucous membrane and the tympanic membrane for each of both sides, as well as for the individual mean figures for the right and left sides. The correlation between the respective values of the right and left sides does not appear to be so marked as might have been expected. In exceptional instances the difference between the values of the two sides has been fairly considerable. For this reason, the mean figure has been calculated for a series obtained by adding together the values of the sides with the highest total sums.

A compilation of the figures for the three series, as to the thickness of the *mucous membrane*, will, be found in Table 1. As will be noticed from that Table, the animals to which no oxygen has been given show, throughout, the highest mean value, the control animals, on the other hand, the lowest one. Where oxygen has been administered the animals reveal a mean between those of the forementioned animal series. The difference between the different series is statistically significant. No difference between the right and left sides has been ascertainable.

Table 1. *A comparison between the different animal series with regard to the thickness of the mucous membrane.*

Group	Number of animals	Right side	Left side	Individual mean of right and left	Side with highest value
1. Control	39[1]	2.1 ± 0.3	1.5 ± 0.2	1.8 ± 0.2	2.3 ± 0.3
2. Oxygen	26	22.3 ± 3.9	19.1 ± 3.3	20.7 ± 2.3	30.5 ± 4.1
3. Without oxygen..	27	42.0 ± 4.1	43.1 ± 3.5	42.6 ± 2.9	52.3 ± 3.2
Difference 1—2	—	20.2 ± 4.0	17.6 ± 3.3	18.9 ± 2.3	28.2 ± 4.1
» 2—3	—	19,7 ± 5.7	24.0 ± 4.8	21.9 ± 3.7	21.8 ± 5.2
» 1—3	—	39.9 ± 4.1	41.6 ± 3.5	40.8 ± 2.9	50.0 ± 3.2

[1] 1 animal with a pronounced pathological value has been eliminated from the series.

Regarding the thickness of the *tympanic membrane* the result of the investigation is identical, i.e., the control animals disclose the lowest value, animals to which oxygen has not been given the highest (see Table 2). The mean value of the animals to which oxygen has been administered is lower than that of the animals without oxygen. The differences are statistically significant, apart from the right side where the difference amounts to twice the mean error. In view of the fact that the other differences between these series are significant, no particular importance need be attributed to the lastmentioned result.

Table 2. *A comparison between the different animal series with regard to the thickness of the tympanic membrane.*

Group	Number of animals	Right side	Left side	Individual mean of right and left	Side with highest value
1. Control	40	0.7 ± 0.04	0.7 ± 0.04	0.7 ± 0.03	0.7 ± 0.04
2. Oxygen	26	3.1 ± 0.7	1.7 ± 0.2	2.4 ± 0.3	3.5 ± 0.6
3. Without oxygen..	27	5.4 ± 1.0	5.7 ± 0.9	5.5 ± 0.8	7.0 ± 0.9
Difference 1—2.....	—	2.4 ± 0.7	1.0 ± 0.2	1.7 ± 0.3	2.8 ± 0.6
» 2—3.....	—	2.3 ± 1.2	4.0 ± 0.9	3.1 ± 0.9	3.5 ± 1.1
» 1—3.....	—	4.7 ± 1.0	5.0 ± 0.8	4.8 ± 0.8	6.3 ± 0.9

As regards the *exudation*, no correlation between the right and left sides has been ascertainable. Nor has any difference in the classification of the groups been found as between the two sides. For these two reasons the material of both sides has been amalgamated. In this manner a bigger material, allowing more definite conclusions, is obtained. The percentage distribution of the cases from one group to another will be seen from Tables 3 and 4. Group I in the control series and group III in the series of animals without oxygen will be found to predominate. The animals to which oxygen has been given occupy a middle position. The difference between the percentage in group I for the control animals and that of the animals which have been given oxygen amounts, in Table 3, to 36.9 ± 7.7 per cent and, in Table 4, to 65.6 ± 6.8 per cent. The difference between the percentages in group III for animals given oxygen and for those not so treated comes, in Table 3, to 49.9 ± 7.0 per cent and, in Table 4, to 24.6 ± 9.4 per cent. Three of the forementioned differences are significant, the fourth approximately so. From this the conclusion may be ventured that the appearance of exudation differs from one animal series to another.

Table 3. *Percentage distribution of the cases in the groups I—III as regards exudation.*

	Number of cases	I	II	III	Total
Control	80	88.8 ± 3.5	11.2 ± 3.5	—	100.0
Oxygen	52	51.9 ± 6.9	46.2 ± 6.9	1.9 ± 1.9	100.0
Without oxygen	54	16.7 ± 5.1	31.5 ± 6.3	51.8 ± 6.8	100.0

Table 4. *Percentage distribution of the cases in the groups I—III as regards exudate behind Shrapnell's membrane.*

	Number of cases	I	II	III	Total
Control	80	92.5 ± 3.0	7.5 ± 3.0	—	100.0
Oxygen	52	26.9 ± 6.1	38.5 ± 6.7	34.6 ± 6.6	100.0
Without oxygen	54	9.3 ± 4.0	31.5 ± 6.3	59.2 ± 6.7	100.0

Discussion.

One observation attracts immediate attention. The sections through the nose reveal in all animals, test animals (= 82 per cent), as well as control animals (= 87 per cent), histologically more or less extensive inflammatory mucous membrane changes in the nose and the paranasal sinuses, in spite of the fact that the animals, when alive, gave no cause to suspect this. Because of earlier experiences the animals were examined daily without disclosing any signs of infection. It is known from the literature that infections of this type occur in the test animals, but so far no figures have been quoted in support of this contention. In "Jaffé: Anatomie und Pathologie der Spontanerkrankungen der kleinen Laboratoriumstiere" (1931), Nussbaum states that he has found spontaneous acute and chronic inflammations in nasal and paranasal sinuses. Griffith and Farris (1942) suggest that infections of the upper air passages are probably the most common of all morbid conditions in adult rats. While the present experiments were proceeding, Kelemen and Sargent (1946) published an interesting observation wholly conforming with the results of my own. They collected 40 rats from different laboratories, all apparently in such a good condition that, as they state "they could be used as control animals". 60 per cent of these animals were then histo-pathologically found to show signs of more or less pronounced inflammatory changes in the nasal mucous membrane. The present investigations afford direct and practical proofs of the difficulties to which this may lead.

This marked predisposition in the animals to infections in the upper air passages manifests itself also in the control material as far as the ears are concerned. In the present material 13 out of 40 control animals disclose bilateral catarrhal changes in the middle ear and a further 4 the same unilaterally, with some exudation and a moderate swelling of the mucous membrane. It is particularly worth stressing that all these animals, like the majority of the test animals at a macroscopic examination, including observation under a preparation microscope, appeared to possess a normal tympanic membrane. In some instances a

yellow-whitish formation was found protruding in the external auditory canal at the locality of Shrapnell's membrane. In these instances an abscess was microscopically noticed at the very spot of the macroscopically observed formation. In the present material suppuration through the tympanic membrane out into the external acoustic canal has been found neither in these animals nor in the most infected ones in the preceding and discontinued experiments. In no instance have any clinical or histological signs appeared of the inner ear being involved in the inflammatory process. In the literature, data regarding spontaneous infections in the middle ear of white rats are rare. Usually they refer to an observation in the animals of a labyrinthitis with its easily noticed clinical manifestations, "twister rats", King, (1939). Nelson and Gowen (1931) have devoted much study to this problem. They observed infections in the middle ear in 40—50 per cent of their breed of rats aged 4.5—6.5 months; growing age caused increased morbidity. These figures conform fairly well to those related above in the present investigation. Nelson also indicated a method to produce a breed exempt from such infections, a procedure which, however, has to be extended over several generations of rats and has, therefore, not been feasible in this connection.

As a matter of course, these two observations, viz., the predisposition for spontaneous infections in the upper air passages and inflammations of the middle ear, unavoidably imply serious sources of error in the tests now performed. Nevertheless, for reasons which will be stated below, the tests have been thought to justify an exhaustive account.

Too much stress cannot be laid on the importance of the infections which will occur in seemingly healthy animals, when a macroscopic autopsy has provided no trace of them, and recourse has necessarily been had to microscopic examination. In another connection difficulties were met with, probably explainable by the very occurrence of these infections in the mucous membranes. In a work published by Aschan (1946), an account was given of the direct and retarding influence of the barotrauma on the ciliary function in the nasal mucous membrane in white rats. Later tests performed on mucous membranes from definitely

not infected animals fail to reveal such an influence. The most likely explanation of the difference in the results appear to be that the animals in the firstmentioned experiment were infected. For purely practical reasons it has proved impossible, at the present time, to secure such optical instruments, film and film-cameras as are desirable from the point of view of a perfect scientific registration. I have, therefore, been unavoidably obliged to discontinue these investigations for the time being.

As the statistical analysis of the material shows, inflammatory changes in the middle ear appear in the control series, as well as in both test series, though considerably more pronounced in the latter case. Quantitative comparisons between these inflammatory changes are not easily performed. Considering, however, the striking parallelism between the four series of measurements contained in the present material, viz., those of the two test series and the control series, there seems to be justification for contending that the barotrauma cannot be said to lack importance with regard to the origin of the increased inflammation in the middle ear and the present tests. The differences between the control series and the test series lie in all the four tables considerably above the limit required for statistical significance. Also a subjective impression of this difference emerges from the direct examination of the preparations. Statistically a difference is also noticeable between the two test series in so far as the animals to which oxygen has been administered during "the flight" show less pronounced changes than those "ascending" into an atmosphere of ordinary composition. Here all the statistical differences in Table 1 lie over and above thrice the mean error of the difference. Three of the four differences in Table 2 are significant, while in one instance the difference amounts to twice the mean error of the difference. One of the differences in Table 4 is only probable. Since, however, they all point in the same direction, the conclusion can be ventured that the administration of oxygen has, with some likelihood, exerted a retarding influence on an inflammation which the barotrauma tends to increase. This conclusion has guided the procedure with regard to my later tests on rabbits.

Summary.

In spite of the fact that the animals had been selected with particular care, by means of a macroscopic clinical examination, the animal material, when examined microscopically, was found to disclose, to a large extent, infections of the upper air passages and inflammations of the middle ear. In the total material, 82 per cent of the animals showed infections of the upper air-ways, the control animals taken by themselves 87 per cent. In addition the latter had otitis media in 43 per cent. Among 40 animals 13 revealed bilateral and another 4 unilateral changes. Thus, a macroscopic examination will not suffice, if white rats are to be used with a view to tests of the upper airways and the middle ear. Such an examination must be supplemented by a microscopic one of all animals, after the conclusion of the experiments, in order to eliminate infections as a source of error.

Notwithstanding that the animal material employed for the present investigation displays infections to such a large extent, certain conclusions from the experiments seem justifiable. The difference in the degree of inflammation in the middle ear in the control animals and the test animals, respectively, is so obvious as to motivate a statistical elucidation of the degree of inflammation in the different series. This has been done by measuring the thickness of the mucous membrane and the tympanic membrane, and further, through a subjective estimation of the nature and amount of the exudations in the measured section, as well as behind Shrapnell's membrane, and a following statistical analysis of the material. It emerges that the inflammatory changes in the test animals are considerably more pronounced than those of the control animals and, also, that they are, with a certain amount of probability, more pronounced in animals to which oxygen has not been administered at the "flights."

V.

Experiments on rabbits

The anatomy of the middle ear and the upper air passages in the rabbit.

The middle ear in the rabbit is well developed, being dominated by a large bulla ossea. Two recesses proceed from the tympanic cavity. The fairly large epitympanic recess reaches a height of 2—3 mm, including in itself the chief part of the auditory ossicles. In addition, there is a smaller posterior recess with a broad communication with the tympanum. The tympanic membrane is encompassed by a ring-shaped crista, strongly projecting into the middle ear, and opening upwards. The pharyngotympanic

Fig. 5. Frontal section through the anterior part of a normal ear of rabbit (control 336 R). Bulla ossea (B.O.) coated with thin mucous membrane without any noteworthy submucosa. The tympanal orifice (E.T.) of the pharyngotympanic tube is clearly visible on the medial wall of the middle ear (M.E.).

tube opens into the anterior part of the medial wall. Laterally to this opening, which resembles a shallow hole, lies a bone ridge. The mucous membrane is everywhere thin, consisting of one or two epithelial strata with the lamina propria directly against the endosteum without any real submucosa, except where the mucous membrane bridges over any unevenness occurring in the underlying bone as, for instance, at the transition from the bulla and the crista to the ear drum.

The pharyngotympanic tube is 4—5 mm long, its construction

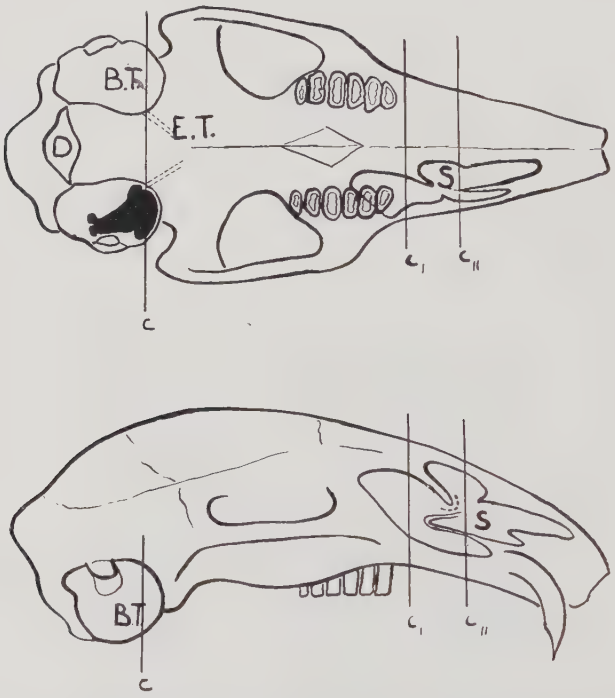

Fig. 6. Semi-schematic figure of skull of rabbit from Röntgenograms. Bulla ossea (B.T.) with shadow of middle ear delineated in top picture. Position of pharyngotympanic tube (E.T.) schematically shown. The line c through the ear indicates direction of the incision at the histo-technical preparation, approximately in the plane in which the mucosal pattern has been made (Fig. 5). In both pictures the exceedingly irregular paranasal sinuses (S) have been outlined. The dotted line in the picture below denotes position of the crescent-shaped sinusal ostium which they have in common. The two lines c_I and c_{II} indicate the direction of incision. The anterior line shows that by one single incision several apparently separate sinusal lumina can be obtained in the same section picture (Fig. 9). The posterior line in the frontal figure gives but one sinusal lumen, but medially conchae, transversely cut, will be noticed (Fig. 10).

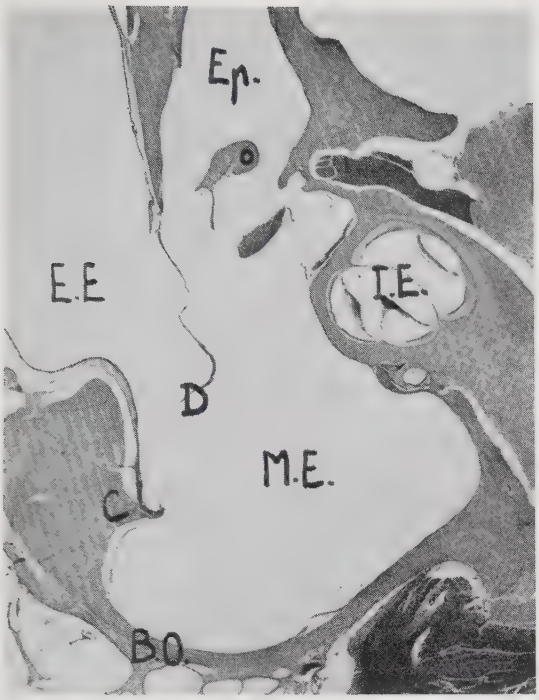

Fig. 7. Frontal section through the middle part of a normal ear of rabbit (control 336 R). The thin tympanic membrane (D) delimits the middle ear (M.E.) from the external acoustic canal (E.E.). The transition of bulla ossea into the crista (C) which embraces the tympanic membrane (D) clearly marks its projection into the middle ear. Also at the transition a thin mucosa is noticed bridging over the irregularities in the underlying bone. At the preparation the epitympanal recess (Ep.) has been opened in all specimens, with a view to obtaining better fixation. Hence the bone defect. The inner ear (I.E.). Auditory ossicle (O).

broadly resembling the same organ in Man. In a transverse section the tubal cartilage embraces, like a hook, a fissure-like lumen. Contrary to statements in the literature (Wolff 1934), the tube of the rabbit is not permanently open. When observing an exposed tympanic membrane at low pressure tests, reductions in pressure will produce small jerky movements in it as "the tubal valve" opens, letting out a portion of air from the middle ear. The difference between the tube of rat and that of rabbit appears most clearly in pictures where, for the sake of comparison, a section through the tube of Man has been added.

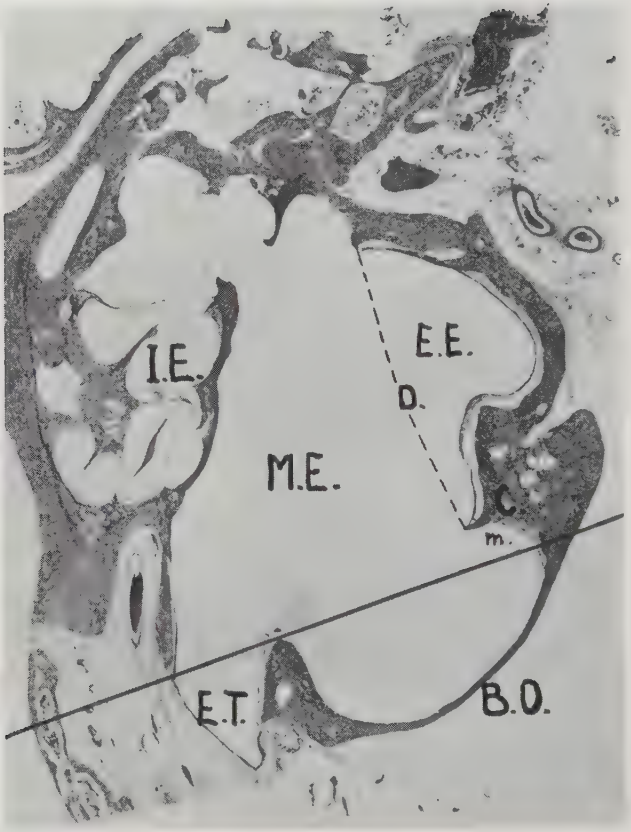

Fig. 8. Horizontal section through a normal ear of rabbit on a level with the orifice of the pharyngotympanic tube. B.O. = bulla ossea. E.E. = external acoustic canal. D. = tympanic membrane, which is missing owing to the histotechnical preparation, here denoted by a broken line. C. = the crista bordering on the tympanic membrane below which m denotes the mucous membrane and such submucosa as will be normally found here. The continuous line shows the direction of incision. Thus, a frontal incision through the middle ear (M.E.) can normally disclose a mucous membrane with submucosa in a small area. I.E. = inner ear.

As will be seen from Figs. 20, 21, 22 there is also a great difference in the development of the m. tensor veli palatini. In Man as well as in the rabbit this muscle is conspicuous, analogously with the tubal function. In the rat with its permanently open pharyngotympanic tube only a few muscular streaks are to be found.

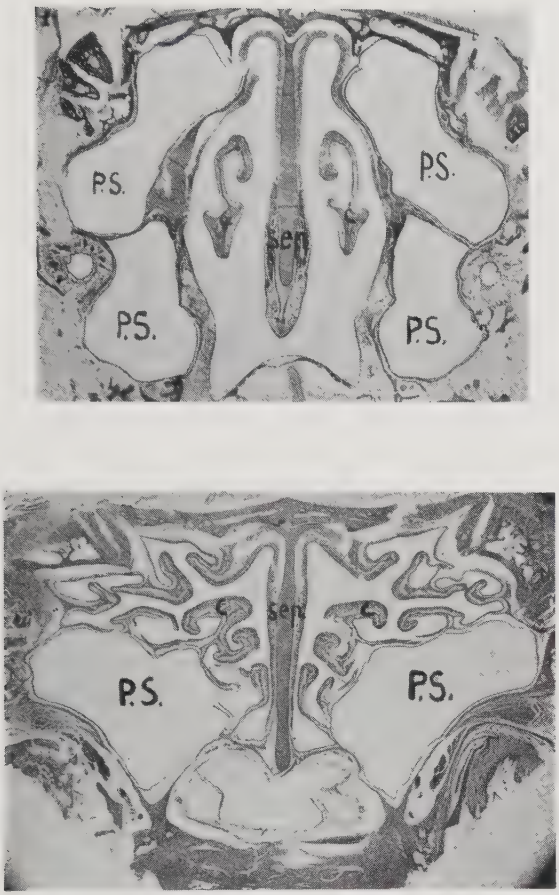

Fig. 9—10. Frontal section through anterior and posterior part (below) of the nose and paranasal sinuses in rabbit. Control animals 437 and 388. The incisions correspond approximately to the two lines C_I and C_{II} in the semi-schematic figure 6. Sep = nasal septum. P.S. = paranasal sinuses. C. = concha. From the upper section it is evident that the irregular form of the paranasal sinuses in one section may produce an impression of several separate lumina. Cp. the foremen-tioned Fig. 6.

The paranasal sinuses are well developed in the rabbit. They consist of a large maxillary cavity which, however, through the bone ridges projecting into it, has assumed an exceedingly irregular aspect. This irregular sinosity opens in its entirety into one single crescent-shaped aperture.

The anatomy is illustrated by semi-schematic figures drawn after röntgenograms (Fig. 6), as well as by the sections through a normal middle ear and nose of rabbit (Figs. 5, 7—10).

Material and methods.

In the course of the initial experiments the standard of the rabbits was found to vary greatly from one breeder to another. Often animals were delivered in which various diseases, such as infections of the upper air passages and otitis media, were discovered at the first examination. In these preceding experiments 167 animals were used and, on the basis of the observations then made, a list of reliable breeders was compiled. By keeping the animals isolated and under observation for a few days, and by separating such animals as might be suspected of any infection, an animal material was secured, exempt from morphological manifestations of infections in the organs to be examined. The histo-pathological control was similar to that of the rat experiments.

One fairly common disease should be mentioned here. In the external auditory canal, in control as well as test animals, small parasites will now and then be found which Mr Åke Holm, Assistant Professsor of the Zoological Institution at Uppsala, has classified as an acarid, psoroptes equi Gervais, varying in nomenclature with the host. The parasite living upon rabbit is called subsp. cuniculi Delafond. In spite of the use of, inter alia, DDT-preparations, it has not been possible to exterminate these parasites but, to judge from the microscopic pictures, they have not caused any changes in the mucous membrane of the middle ear that could constitute any source of error in the tests. However, in these cases a hyperemia will occur in the tympanic membrane, the significance of which will be discussed later.

By means of the preceding experiments a form of procedure was established with a view to produce the very changes that were to be studied. In the low pressure chamber tests it was found that the animals could not be continuously exposed much beyond the actually used time, i.e. 6 hours, without risking that they would die in the course of the tests or through a pneumonia-like

disease between the flights. The animals were found to endure high oxygen pressures at 1 atmosphere better. For this reason a continuous exposition has been found more suitable whenever, increased oxygen pressures have been unconnected with reductions in pressure in a low pressure chamber.

All test and control animals have been killed and histo-technically treated in the same manner. While in a light intravenous numal narcosis (about 1.5 cc), the animals have been decapitated by scissors immediately caudally to the occipital bone. The skull was flayed and the lower jaw removed except for a part close to the maxillary joint, this in order not to damage the pharyngotympanic tube and the middle ear. The cranial cavity was opened and, to facilitate fixation, the brain was extracted. A piece of one of the lungs was simultaneously excised. Thereby it was possible to ascertain the general appearance of these organs and the possible presence of any exudations in the serous cavities. All the material was fixed in a 10 per cent formalin solution. The skull was then decalcified in 5 per cent nitric acid. After 72—96 hours' decalcification it was easier to cut the preparations, without any risk of injuring the organs which were to be sectioned. By means of two frontal incisions through the anterior part of the cranium, part of the nose, with the paranasal sinuses, was excised. Another frontal incision was performed in front of the tubal orifices. This specimen was divided by a median incision. The latter section surface was then used as a means of orientation for the sectioning which was to be done perpendicularly to the median line. Thus each ear was sectioned separately. All musculature, etc., of no significance in this connection was removed. With a view to obtaining better decalcification and embedding, also the epitympanum was opened, by means of a superficial tangential incision. After repeated decalcification embedding was performed in the ordinary way in paraffin.

From the pulmonary and nasal preparations only one section, 10 μ thick, was taken. From the ear preparations sections, 15 μ thick, were made, every twentyfifth being preserved, i.e. one section per 0.375 mm of the preparation. Thus, on an average 15—20 frontal sections were obtained through each middle ear, fully sufficient to provide a satisfactory and comprehensive

picture of any possible histo-pathological changes in any of the different parts of the middle ear. All sections were stained with hematoxylin-eosin.

The apparatus was described in connection with the rat experiments (see p. 22). For the purpose of the oxygen deficiency tests with a maintained atmospheric pressure, an evacuation pump with a capacity of about 8 l/min was coupled to the chamber. The air was mixed with nitrogen in a bottle of water before being forced into the chamber. By this means a very slightly lowered pressure occurred in the chamber, not exceeding 2 mm Hg, which will be totally disregarded here. The composition of the air in the chamber was repeatedly tested and analysed in a modification of Haldane's apparatus for gasometric analysis suggested by Enghoff (1946).

At the experiments with increased oxygen partial pressures at atmospheric total gas-pressure the gas-container was coupled directly to the closed chamber and, forced by the pressure in the gas-container, the gas was made to flow through the chamber with a velocity of about 5 l/min. The gas mixture emitted from the chamber was subjected to analysis. Before this the samples were diluted with N_2 in the apparatus, since this had proved most suitable with a view to the gradation of the gas burette. At oxygen experiments combined with low pressure tests analyses could only take place during the first test hour, since after that time the gas from the pump was mingled with "oil-smoke", probably originating in oxidation processes in the oil of the pump, resulting in an adulteration and a discontinuation of the analysis.

In all instances the room temperature has been 18—23° C. The humidity of the chamber has kept at 80—100 per cent. At the experiments with increased or decreased oxygen pressures the gas taken from a container was allowed to enter the chamber only after having passed through a wash bottle with water.

For practical, economic and other, reasons the test material has not been photographed and reproduced in its entirety, nor should such a procedure, if adopted, in any way have improved the comprehensiveness or the possibilities of comparisons between different test objects. As the reproductions of the micro-photos

will show the results and the consequent conclusions are determined in the first place by the qualitative changes.

From each test series only one typical case, supplemented by several detail pictures from the same animal and others, has been published. In addition to the micro-photos a section from each ear has been projected in a drawing apparatus. The mucosal picture is shown in black, while such exudation as may have appeared has merely been marked by contour lines. The section has been taken from the anterior part of the middle ear, since the tympanic orifice of the pharyngotympanic tube offers an easily available point of orientation and, further, the mucosal pictures in this particular part mostly disclose a far less complicated figure than sections otherwise situated. In Fig. 6, and also in Fig. 8, the line c denotes the approximate position of this section.

On account of oblique sectioning in a few cases, the apparent thickness of a mucous membrane is not always an exact expression of the actual mucosal thickness. Defects and coarse deformations are unavoidable in preparations, owing to histo-technical difficulties. For this reason it has occasionally proved necessary to draw from an adjoining section. The forementioned oblique sectioning reveals itself either by the fact that the crista of the tympanic membrane has been contacted, a distinct, lighter spot in the mucosal shadow being noticeable, for instance in 314 L, or through a considerable shrinkage in the transverse section. In the latter instance, a section taken from a part of the preparation situated further in, of the same diagonal measure as that of other normally cut specimens, has been chosen. The caption of such a reproduction will indicate when this has happened. The almost spherical shape of the anterior part of the middle ear, owing to the bulla ossea, is an additional factor modifying the incision error and justifying this procedure. The result of a series of drawings of adjoining sections will show that only incisions of a particularly marked obliquity will produce pictures that are directly misleading.

It should, at the same time, be borne in mind that the principal purpose of these reproductions is not to serve any quantitative comparisons between the different test series. They must be

viewed, first of all, in the light of a histo-pathological analysis. Any mucosal swelling and possible exudation are but slightly significant of the type and degree of changes in the mucous membranes of the respective middle ears, as seen, for instance, in 302 R, the reproduction of which discloses comparatively inconsiderable changes, while Fig. 24 reveals all the later recorded qualitative characteristics. Also 356 R and 362 R, Figs. 30 and 31, appear essentially different according to the reproductions, while their microscopical pictures are qualitatively almost entirely identical. In so far as any two test series have been subjected to a quantitative comparison, the patho-anatomical changes have been so differently pronounced as to render the previously specified sources of error wholly unimportant. Attempts at elucidating these differences statistically, as in connection with the rat experiments, viz., by measuring the mucosal thickness, were attended by sources of error of such a size as to make the method preferred here decidedly superior, considering the obviousness of the differences in these instances. Planimetrical determinations would have to be worked out in a way similar to that above. Such determinations have been computed, since they provide a statistical elucidation of the considerable differences in the mucosal swelling in the animals 451—462, as against the other series.

Below, a separate account will be given of the different tests, including, first, the changes in the middle ear, then, those in the nose and the paranasal sinuses and, finally, the lung changes.

111 rabbits of both sexes were used for the definitive experiments. The weight of the animals varied from 1.8 to 2.3 kg. Out of the forementioned number 45 animals were employed as controls. The remaining ones were divided into four test series, as follows:

1) Low pressure chamber tests with normal composition of the atmosphere. Reduction of pressure 400 mm Hg 6 hours daily for 10 consecutive days . 29 animals
2) Oxygen deficiency tests. 9—10 volume per cent O_2 given 6 hours daily for 10 consecutive days ... 13 animals
3) Increased oxygen partial pressure. 80—90 volume per cent O_2 at 1 atmosphere given for 60 hours 12 animals

4) Increased oxygen partial pressure. 80—90 volume per cent O_2 combined with low pressure chamber tests as in paragraph 1 ..... 12 animals

Changes in the mucous membrane of the middle ear.

Low pressure chamber tests with normal composition of the atmosphere.

For 6 hours daily during 10 consecutive days 29 animals were exposed to pressure reductions of 400 mm Hg. Here mention will be made only of the fact that the strong airing of the low pressure chamber, 30—40 l/min, prevented the occurrence within the chamber of any noteworthy increase in the carbon dioxide concentrations. This will be seen from the appended tabular compilation of carbon dioxide analyses of the outflowing air. It should be noted that the carbon dioxide concentration has been kept at about 1 per cent or less.

Table 5. *Gas analyses in connection with low pressure chamber tests.*

Animals Nos.	Volume per cent CO_2			
	Min.	Max.	Mean	Standard deviation
301—304.....	0.40	1.20	0.81	0.20
305—308.....	0.55	0.80	0.67	0.09
309—311.....	0.32	1.10	0.75	0.25
312—315.....	0.62	1.05	0.81	0.13
Total	0.32	1.20	0.77	0.19

15 animals, Nos 301—315, were killed immediately after their last flight, the others 4, 10, 15 or 20 days later, always four animals simultaneously, apart from the last time, when only two animals remained. All animals endured the flights without any manifest troubles.

The animals Nos 301—315 have been used for studies of the produced changes, the remaining 316—329 for ascertaining the length of time before the changes reappear. Below, these two series will be dealt with separately.

a) Apart from a certain hyperemia in Shrapnell's membrane, the animals Nos 301—315 did not, at autopsy, reveal any definite macroscopic changes. Sometimes it proved impossible to obtain a clear picture of the tympanic membrane, since it was obscured by parasites of the previously described type (312 R, 303 R and 304 L), clotted together in excretions. The tympanic membrane of 307 R was damaged, while the external auditory canal was being cleared from parasites.

Microscopically all animals showed mucosal changes in the middle ear, except 303 L which does not noticeably differ from the control animals. The changes are not equally pronounced in all parts of the middle ear. As a rule, they are particularly marked in the mucous membrane on the inner side of the bulla ossea except around the tubal orifice. Changes are but rarely found in the mucous membrane above the promontory. The same uneven distribution of the changes in the preparation applies to exudations. Owing to sedimentation of cells in the exudate, and shrivelling during the histological analysis, all sections from each ear had to be examined before a true conception of the type and extent of the changes could be formed.

The mucosal changes are in the first place characterized by edema, hyperemia and hemorrhage. The edema is very differently pronounced. It occurs in the mucosa, sometimes like granular masses, sometimes taking the shape of an even, homogeneous

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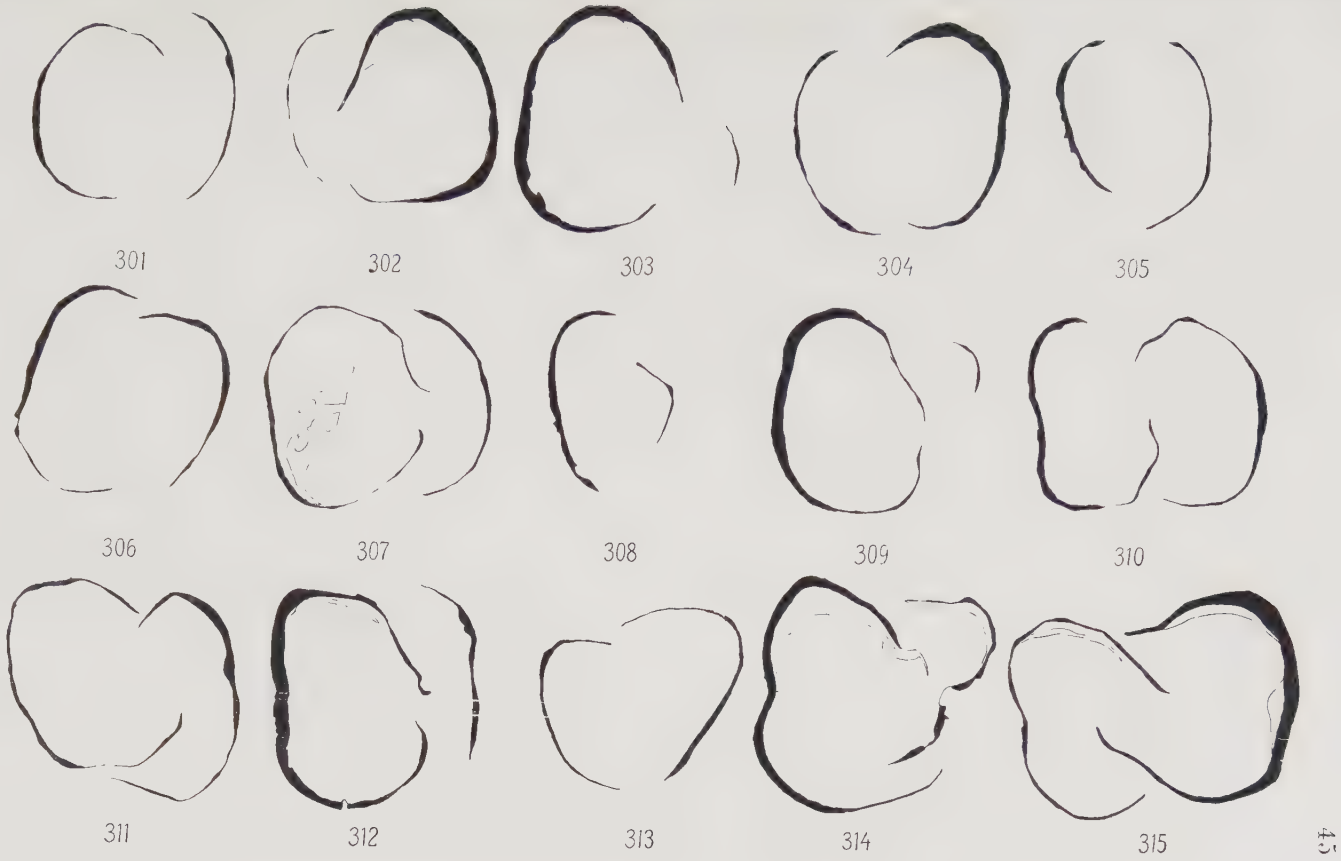
Fig. 11. Mucosal reproductions from the animals 301—315, killed immediately after their last flight in low pressure chamber. Magnification 3 times. In all instances the distinguishing figure indicates two reproductions, the first of the right, the second of the left ear of the respective animals. The quantitative variability in the changes is striking, from one animal to another, as well as from the right to the left side in the same test animal. 314 L shows a light spot in the shadow, caused by the crista of the tympanic membrane, this picture being typical of oblique sections. 309 R and 310 R oblique sections, the drawn section from a part further in. 311 R drawn from an adjoining section, since the topographically most suitable section had been injured in the course of the histo-technical preparation.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mass full of blisters, like bright spots. Fig. 24 from animal 302 R shows all the different appearances of the edema. Now and then the edema will altogether dominate the histological picture, e.g., Nos 313 R and L and 314 R. Also the hyperemia will greatly vary. When the mucosal swelling is particularly pronounced, the vessels will be found to lie in two strata, one subepithelially, the other deeper down in the submucosa, close to the endosteum of the bulla ossea (Fig. 23, 26, 303 R and 309 R). Whenever the mucosal swelling is but moderately pronounced, as, e.g., 302 R, 307 L, 308 L and 315 R, the hyperemia will, as a rule, predominate. Occasionally, as in the instance of 301 R, 308 R and 314 L, big, widened endothelial spatia will be noticed in the mucous membrane, mostly empty, but sometimes containing a spot of blood or a granular coagulated exudate with a single cell or so, i.e. dilated blood or lymph vessels, due to local stasis, a matter to be dealt with in connection with the following description of the animals 316—329. No special changes in the epithelium against the tympanic cavity have been noticed, apart from an edematous swelling whenever the edema in the mucosa has been strongly pronounced.

The hemorrhage has without exception taken the form of diapedesis. Also in this instance all possible quantitative variations occur, from an isolated red blood corpuscle or two perivascularly (Figs. 23 c and 25, 303 R and 307 R) to such an intense soaking of the entire mucous membrane that the vessel emitting the blood has become invisible, (Fig. 26, 309 R). In rare instances bleeding has taken place into the tympanic cavity, though never to any noteworthy extent. As a rule, it appears like a thin accumulation on the epithelium (302 L, 313 L, 307 R, 308 R and 312 R). Only in three cases has it taken the shape of clots of red blood corpuscles in exudations in the tympanic cavity (302 R, 313 L and 314 R).

As will be seen from the reproductions (302 L, 303 R, 307 R, 309 R, 312 R, 314 R and L and 315 R and L) exudates will vary in amount in the middle ear. In the epitympanum such changes occur in 23 of 30 cases.

The cellular reaction in the mucous membrane attracts particular attention. Broadly speaking, apart from the red blood

corpuscles due to hemorrhage, it has been but slightly pronounced, confining itself to solitary mono- or lymphocytic cellular elements, without any agglomeration or infiltration. No perivascular reaction, indicating any inflammatory vascular lesion as a cause of the hemorrhage is noticeable. Nor around the hemorrhage in the mucosa does any cellular reaction occur. In the above-mentioned cases, where blood is present on the epithelium of the tympanic cavity, a light epithelial or subepithelial reaction, chiefly of a lymphocytic nature, is now and then observed.

In the exudation in the middle ear cells are sparse. Most often, they are collected at one edge of the exudation, forming a sort of cellular line of junction with the underlying tissue (Fig. 26 309 R). Around the hemorrhages in the exudation (302 R, 313 L and 314 R) a mixed lympho- and polynuclear cell reaction is visible. Only in one instance, viz., 307 R, is the cell reaction in certain parts of the exudation, chiefly polynuclear and intense enough to suggest the possibility of an infection. Still, there is no mucosal reaction of a corresponding type. Also this preparation was damaged when being made ready and there is a risk of artefacts.

The changes in the tympanic membrane are histologically inconsiderable. A certain hyperemia is noticeable in Shrapnell's membrane. Also the control animals display similar pictures. Such hyperemia in the tympanic membrane itself as occasionally occurs is mostly combined with the appearance of parasites in the external ear and may happen also in control animals with the same affection. The existence of such parasites thus prevents any conclusions as to the vascularization of the tympanic membrane.

In sum, the low pressure chamber tests have produced mucosal changes in the middle ear, of a non-inflammatory nature, histologically characterized by edema, hyperemia, bleeding per diapedesis and transudation into the tympanic cavity.

b) As regards the animals Nos 316—329, the purpose was to ascertain the length of time required for a restitution of the changes observed in the previous series and the particular form of the regress and, further, to watch for special changes, if any.

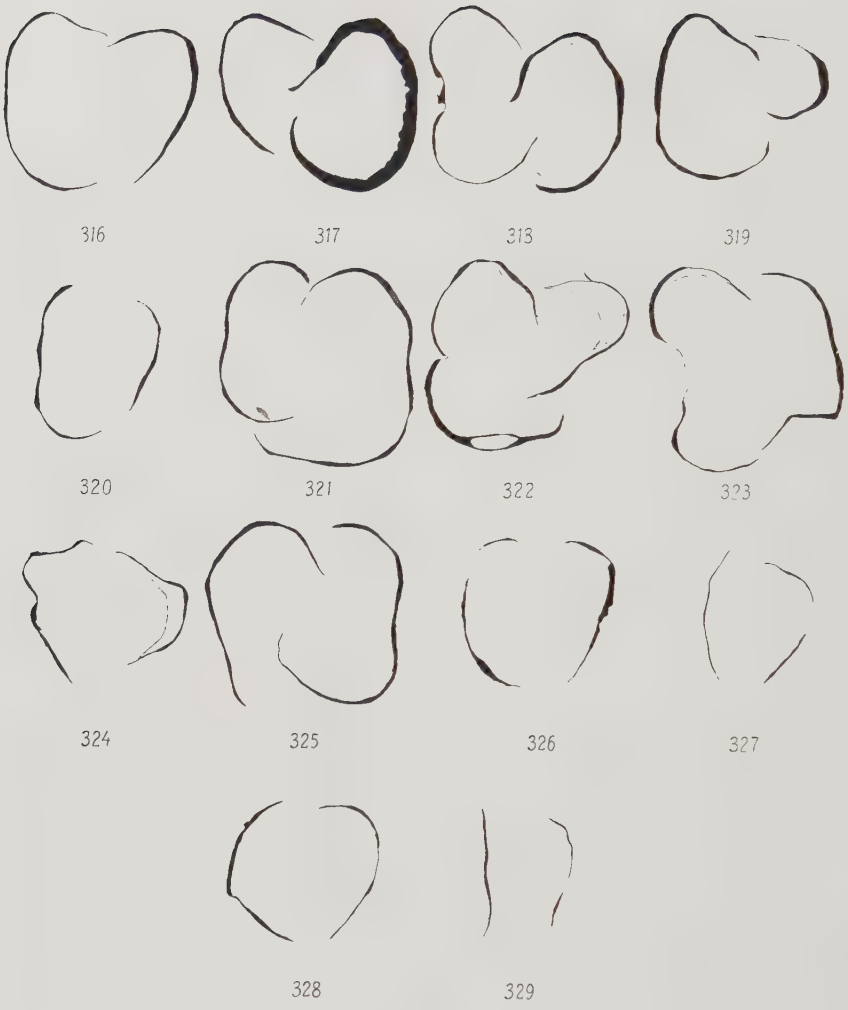

Fig. 12. Mucosal reproductions from the animals, killed 96 hours (316—319), 240 hours (320—323), 360 hours (324—327) and 480 hours (328—329), respectively, after their last flight in low pressure chamber. Magnification 2.5 times. The reproductions have been arranged into groups, animals killed at one and the same time being placed together. 318 R, 322 R and 323 R in oblique sections. The irregularities in 323 L and 324 R due to artefacts occurring during the histotechnical preparation.

The lack of knowledge regarding the actual degree of the changes existing in the ears in immediate connection with the last flight has detracted from the value of these tests, in view of the considerable individual variations which, as previously stated, may appear in one and the same trauma.

316—319 were killed 4 days after their last flight in the low pressure chamber. In all the animals mucosal changes, of fundamentally the same characteristics as those mentioned before, are found. 318 L shows the beginning of a restitution. The mucosal swelling remains but the mucosa has an even, dense appearance, with an abundance of big, empty endothelial spatia of lymph or blood vessels. The whole mucous membrane reveals en evenly distributed, extremely moderate mononuclear cell reaction (Fig. 27).

Microscopically 320—323 disclose a very moderate mucosal swelling. The hyperemia remains but the hemorrhage has changed its character. Even though bleeding of the same type as previously occurs, it usually manifests itself as more massive, distinctly defined clots of red blood corpuscles. Around these clots there is no sign whatever of any cellular reaction (Fig. 28). In this particular instance the edema appears considerably reduced, a fact which, no doubt, has contributed to the special aspect of the hemorrhage. Varying amounts of big, wide blood and lymph vessels are noticed. The marked light spot in the mucosal shadow in the reproduction of 322 R is due to an additional bone ridge in the middle ear of that animal and a consequent pouch-like formation which has been cut obliquely, thus producing this obscure picture. 321 R shows an old hemorrhage, partly in the process of organization, partly situated in an exudation with a moderate, almost exclusively lymphatic or monocytic cell reaction.

324—327 show further regress. The mucous membrane is thin, sharply delineated, with a mucosa a little more cellular than usual. 324 L, in addition, discloses a slight number of red blood corpuscles close to the auditory ossicles, partly in a state of disintegration with an inconsiderable mono- and lymphocytic reaction. In 326 R the previously described spatia of lymph and blood vessels appear strongly pronounced like a vascular ball with densely placed vascular spatia without any contents (Fig. 29).

The patho-anatomical significance of those, also previously observed, formations is not easily defined. The following reasoning, however, may, perhaps offer an explanation: The middle ear is a cavity, altogether delimited by bones. All efferent vessels must therefore pass through osseous canals with a consequent restricted possibility to adapt, i.e. increase, the vascular transverse section, in the event of affections in the middle ear and its mucous membrane. This will probably explain the occurrence of a local stasis in the mucous membrane with a following vascular dilatation, as stated above, in the event of the previously described mucosal changes.

Microscopically 328 and 329 reveal but slight mucosal changes, differing merely by a somewhat more dense mucosa and an inconsiderable hyperemia from what may now and then occur in a control animal. Still, in 329, a small hemorrhage, with red blood corpuscles in the course of disintegration, and the faint mono-lymphocytic cell reaction repeatedly referred to above, will be noticed.

Hence, only in animals killed 10 days after their last flight signs of a regress in the mucosal swelling will manifest itself, in the first place through a reduced edema and a sharper delineation of the earlier diffuse bleedings per diapedesis. On the twentieth day, but not before, the changes are so far restituted that the mucosal picture does not to any noteworthy degree histologically differ from that of the control animals. However, traces of a small hemorrhage in a state of decomposition, among the auditory ossicles in one ear, show that the regress is as yet incomplete. Bleeding into the tympanic cavity alone seems to cause a reactive cellular irritation with mono- and lymphocytic cell elements around the hemorrhage. In the mucosa the hemorrhage discloses no such irritation. The red blood corpuscles decompose without any local reaction and disappear.

Oxygen deficiency tests, 9—10 volume per cent O_2 at 1 atmosphere.

The prerequisites of these experiments are the same as those previously stated. In the low pressure chamber the animals were exposed, 4—5 at a time, for 6 hours daily during 10 consecutive

days, to an oxygen concentration of 9—10 volume per cent. With the air circulation prevailing in the chamber, viz., about 8 l/min, no noteworthy increases in the carbon dioxide concentrations occurred. Further, a number of Petri's dishes with potassic lye had been placed in the cubic annex of the chamber, as well as in a small barred cage within the chamber. In this way a more complicated technical apparatus, for the purpose of keeping the carbon dioxide concentrations down, became superfluous. The mean values of the gas analyses will be found in the appended table, where the oxygen and carbon dioxide concentrations are stated in volume per cent (see Table 6).

Table 6. *Gas analyses in oxygen deficiency tests, 9—10 volume per cent O_2 at 1 atmosphere.*

Animals Nos.	Volume per cent CO_2				Volume per cent O_2			
	Min.	Max.	Mean	Standard deviation	Min.	Max.	Mean	Standard deviation
351—354....	0.31	1.45	0.67	0.23	8.41	11.21	9.5	0.5
355—359....	0.21	1.37	0.67	0.33	8.26	11.35	9.6	0.6
360—363....	0.30	2.31	0.72	0.40	7.92	10.37	9.4	0.5
Total	0.21	2.31	0.68	0.33	7.92	11.35	9.5	0.5

All the animals endured the oxygen deficiency without any conspicuous troubles during or after the exposition.

The experiment includes the animals 351—363. Macroscopically they displayed the same picture as the animals 301—315 in the low pressure chamber experiments. In a few isolated cases a slight hyperemia in Shrapnell's membrane was noticeable. In several instances this hyperemia was, however, hidden by secretions and parasites of the type referred to before. In two middle ears, viz., 352 L and 358 R, no special pathological characteristics were microscopically discernible.

The remaining mucous membranes of the middle ears disclose, on the whole, a picture identical with that of the animals 301—315, with the same histo-pathological characteristics, viz., edema, hyperemia, bleeding per diapedesis and transudation into the tympanic

cavity. As before, an inflammatory aspect is totally absent from the picture (Fig. 32). In five instances (352 R, 355 R and L, 361 L and 362 L) an exudation, as seen from the reproductions, occurs in the anterior part of the tympanic cavity. 13 out of 26 had a granular, coagulated exudate in the epitympanum. In five cases only a faint cell reaction is found in the exudation, which is always a mixture of a mono- or lymphocytic nature. Here and there (for instance, 356 R and L) the hemorrhage is extremely pronounced. The mucosa is diffusely soaked with varying amounts of red blood corpuscles, covering all other structures (Fig. 30). Notwithstanding the marked qualitative histo-pathological changes the mucosal swelling is, in these cases, not so pronounced. This again emphasizes the fact that the tests must, in the first place, be interpreted and judged according to the qualitative histological pictures, not quantitatively (cp. the reproductions of 356 R and 362 R, in Fig. 13 as compared with micro-photos Figs. 30 and 31).

Increased oxygen partial pressure, 80—90 volume per cent O_2 at 1 atmosphere.

Also here an account has already been submitted of the apparatus and prerequisites of the experiment. No special arrangements, with a view to keeping the carbon dioxide concentrations low, have been required in this instance. A source of error with regard to the determination of the gas concentrations is to be found in the dilution with N_2, which was performed in order to obtain values suitable to the gas burette, since the burette is adapted to concentrations below 25 volume per cent. Thus, the risk of admixture of air has to be taken into account, the cited values being somewhat understated. The determinations of oxygen taken direct from the containers serve as a control of this source of error. It is not of such dimensions as to play any noteworthy

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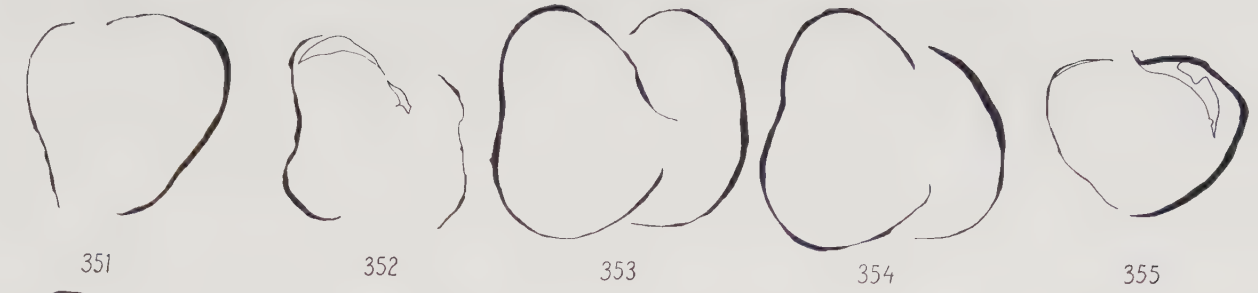
Fig. 13. Mucosal reproductions from oxygen deficiency tests. Magnification 3 times. 352 R and 357 R in slightly oblique section. To 362 R belongs a small transudate, situated in the tubal orifice itself. It has been indicated in order to illustrate the topography.



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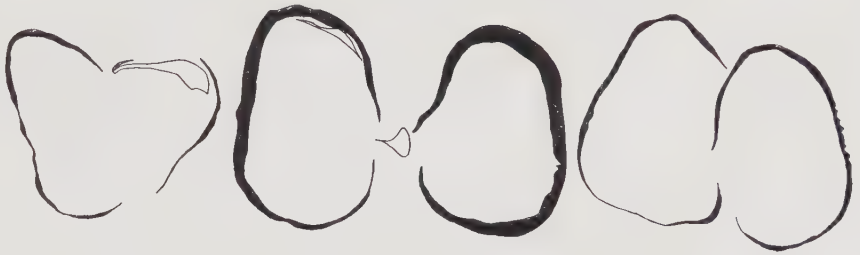

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part in this connection. This is obvious from the fact that 10 determinations of oxygen taken straight from the gas container produced a mean of 23.8 volume per cent in place of the expected 25. Thus, the dilution error implies an average deviation of 4.8 volume per cent with a standard deviation of 1.4. An additional admixture of air has, undoubtedly, taken place in the closed chamber due to its not being absolutely tight. The extent of such admixture is seen from the figures of performed gas analyses computed in the table. None of the values have been corrected with regard to the above-mentioned dilution error.

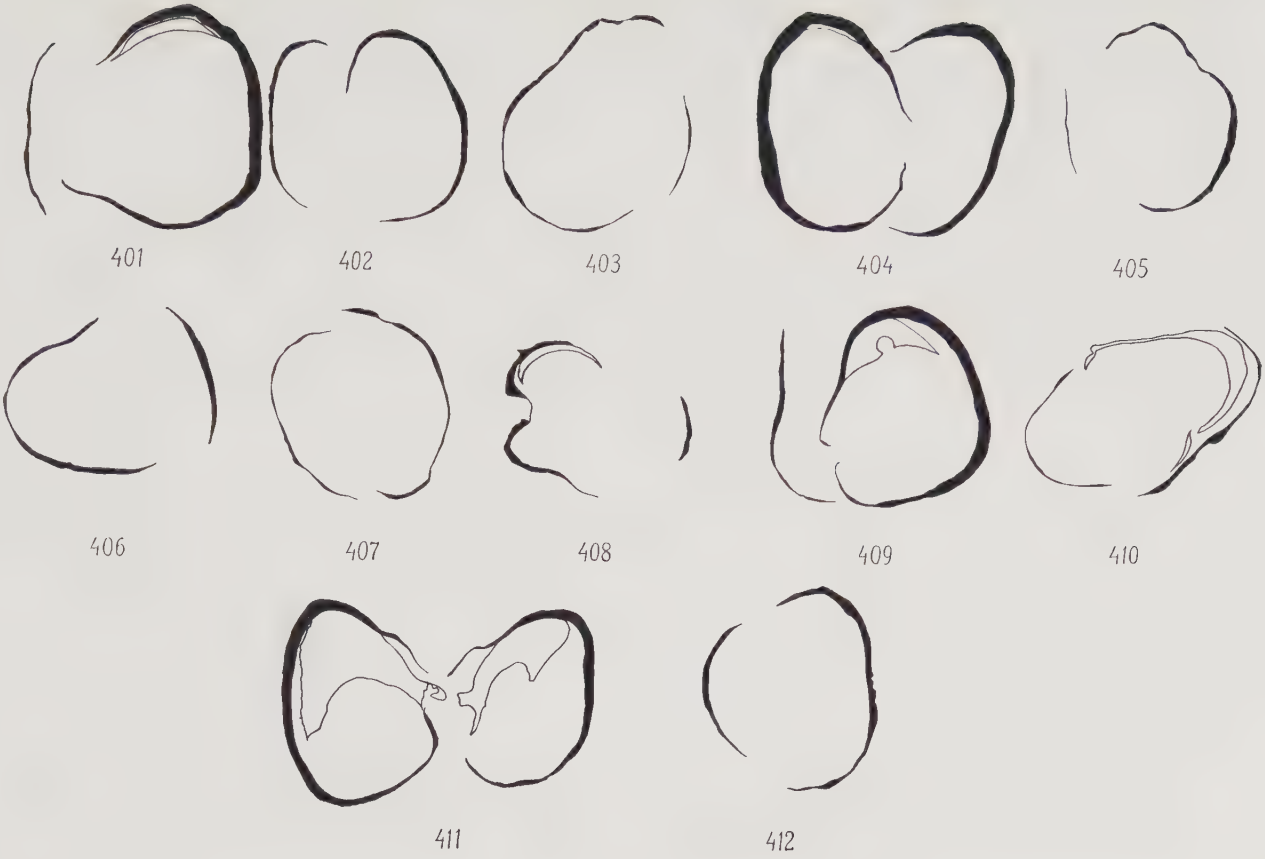
Table 7. *Gas analyses in tests with increased oxygen partial pressure at 1 asmosphere.*

Animals Nos.	Volume per cent CO_2 after dilution with 3 parts N_2				Volume per cent O_2 after dilution with 3 parts N_2			
	Min.	Max.	Mean	Standard deviation	Min.	Max.	Mean	Standard deviation
401—404....	0.05	0.14	0.07	0.03	20.1	22.2	21.4	0.7
405—409....	0.05	0.12	0.07	0.03	19.3	21.9	20.5	0.7
410—412....	0.01	0.25	0.08	0.04	21.1	23.0	22.2	0.5
Total	0.01	0.25	0.07	0.03	19.3	23.0	21.3	0.9

The volume percentage of carbon dioxide has been kept < 1, and that of oxygen has, on an average, been 85. Thus, the essential fact is that the oxygen concentrations have been kept at 80—90 volume per cent.

The series comprises the animals 401—412. Macroscopically the same diffuse findings, as described in the previous experiments, are discovered in the ears. Microscopically three ears, 403 L, 405 R and 408 L, display no definite changes. In the other cases the same quantitatively uneven distribution of the mucosal changes occur, with identical qualitative characteristics,

Fig. 14. Mucosal reproductions from the animals 401—412. Oxygen poisoning. Magnification 3 times. Oblique section 408 R. The animals killed after being exposed for 60 hours to 0.8—0.9 atmosphere oxygen.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viz., edema, hyperemia, bleeding per diapedesis and transudation (Figs. 34, 35). The variations from one animal to another within the series are, if possible, even more pronounced than in the preceding test series, while the changes in one and the same animal do not seem to vary quite so much. In the reproductions corresponding to the anterior sections, transudations occur in 8 instances. 13 out of 24 ears show a varying amount of exudation, of the same character as earlier, in the epitympanum. In 411 R and L the exudation is extremely pronounced, while, at the same time, the mucosal changes are entirely dominated by edemas. Some hyperemia and, also, bleeding per diapedesis is noted. They are, however, small-sized, and occur sparsely. The edema has also contacted such mucous membrane as covers the auditory ossicles and their ligaments, the muscle stapedius and the mucosal folds in the epitympanum. Here the edema is pronounced to such a degree that the motley picture of the exudation in this region of the section of 411 R (Fig. 33) becomes intelligible only after a comparison between several adjoining sections.

Increased oxygen partial pressure in low pressure chamber tests.

The prerequisites of the experiments have already been roughly stated. When the reduction in pressure began, the oxygen was at once connected with the valvular inlet. When the pressure in the chamber had been reduced 400 mm Hg, samples of the gas emitted from the pump were taken for analysis. Before the analyses the samples were diluted with N_2 in the apparatus in the way previously stated. The before-mentioned oil-smoke, in the gas issuing from the pump, caused a technical difficulty by rendering any analysis impossible after the first test hour. There is, however, no reason to suspect that any material deviations have taken place during the latter part of the test.

Macroscopically the same findings as in earlier tests were noted, viz., a slight hyperemia of Shrapnell's membrane. Here it has to be borne in mind, however, that in several instances the

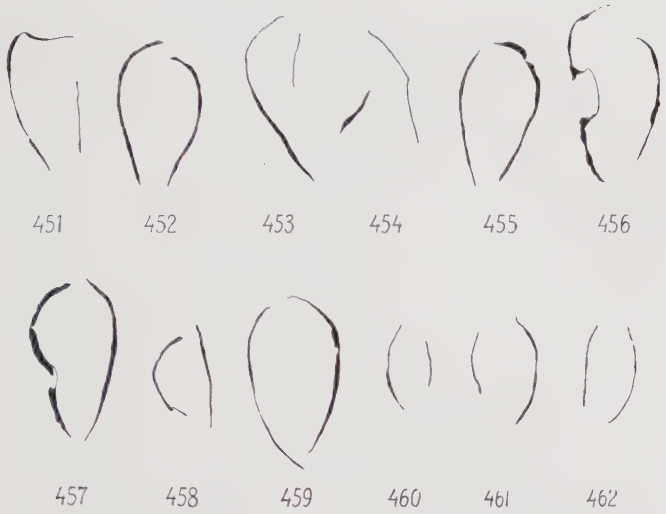

Fig. 15. Mucosal reproductions from the animals 451—462. Oxygen poisoning in low pressure chamber tests. Magnification 3 times. Though the quantitative difference (cp. the other test series) conspicuous, the histo-pathological picture decisive. Oblique section of 456 R and 457 R.

Table 8. *Gas analyses in tests with increased volume per cent O_2 in low pressure chamber experiments.*

Animals Nos.	Volume per cent CO_2 after dilution with 3 parts N_2				Volume per cent O_2 after dilution with 3 parts N_2			
	Min.	Max.	Mean	Standard deviation	Min.	Max.	Mean	Standard deviation
451—454....	0.05	0.34	0.17	0.06	17.6	24.1	22.2	1.4
455—458....	0.05	0.36	0.17	0.06	17.1	24.0	22.2	1.7
459—462....	0.05	0.26	0.15	0.05	18.2	23.6	21.3	1.3
Total	0.05	0.36	0.17	0.06	17.1	24.1	21.9	1.6

tympanic membrane has not been discernible, on account of parasites and the secretion thus caused in the auditory canal.

Microscopically the most conspicuous feature is the sparseness of pronounced changes as against the preceding tests. The great majority of the middle ears disclose entirely normal conditions or but a diminutive increase of the submucosa, corresponding

to the bulla-crista curvature, where this is normally more or less pronounced. No noteworthy exudations are noticeable. However, six ears reveal small amounts of epitympanic exudate (451 R, 454 R, 455 L, 456 R and L, 461 L), though by no means comparable to those in previous test series. No cells are discoverable in this exudation. Bleeding per diapedesis occurs, to a small extent, in two cases only (455 R and 459 R). No particularly noteworthy hyperemia is noticed anywhere. The hyperemia disclosed in 452 R and L is extremely moderate, as compared with changes observed earlier in other test series. Thus only 10 out of 24 middle ears show changes which may be termed pathological in comparison with the control animals. Nevertheless, the changes are so much less pronounced than in the previous series that, without any measuring, a significant qualitative difference can be stated to occur as against the other tests, combined with a markedly quantitative one.

The control animals.

In none of the 46 control animals have any inflammatory mucosal changes appeared, nor any changes of the above described type.

Planimetric determinations of the sections drawn in the reproductions.

The planimetric determinations have been computed on the basis of the original drawings of the sections in their 10 times' magnification, previously reproduced in a minor scale (Figs. 11, 13, 14 and 15). In view of the fact that only comparisons between the series in their respective entirety have been aimed at, the obtained planimetric values have not been corrected to the actual ones. The method error has been determined by means of twofold measures of 30 individuals, amounting to 0.21 with an average area of 6.2, i.e. about 3 per cent of the surface. Consequently, the significance must be accepted as satisfactory.

The different test series disclose the following means with regard to the size of the surface of the mucosal reproductions:

Animals Nos 301—315	6.2±0.84
351—363	6.4±0.96
401—412	5.7±1.12
451—462	1.2±0.16

The difference between, on the one hand, the group 451—462 and, on the other, the three other groups is everywhere statistically significant, a fact which, of course, speaks in support of the conclusions arrived at in this investigation, though, as previously stated, the qualitative changes will in the first place decide the discussion and results.

Changes in the nose and the paranasal sinuses.

Low pressure chamber tests with normal composition of the atmosphere.

a) Of the animals Nos 301—315 nine show no histologically ascertainable changes, while two (303 and 307) disclose less pronounced and four (302, 306, 309 and 311) pronounced changes. Irrespective of variations in degree, all these can be summarized as follows. In the paranasal sinuses, and in two instances also in the nose, an exudation will be noticed which, when subjected to fixation, coagulates, revealing a fine-granular picture in the section, with but a sparse amount of cells of a lymphocytic nature. In no case is there any question of an inflammatory exudate. The mucous membranes are characterized by hyperemia and edema, most markedly in the mucous membrane that coats the conchae. Here and there extremely insignificant signs of bleeding per diapedesis are noticeable (Fig. 36). The animal 303 shows in one sinus a minor hemorrhage above the epithelium. Around it is an exudation without cells, of the same granular appearance as otherwise. Neither here nor in other places is any cellular reaction in the mucous membrane in particular evidence. The solitary polynuclear or lymphocytic cells observable in the mucous membranes do not occur more frequently than is usual in the control animals. Consequently, the changes are not of an inflammatory nature.

b) Of the animals Nos 316—329 three display histological changes in the nose and the paranasal sinuses. Fundamentally No 316 discloses the same picture as that previously described. In the animal 317 the picture differs slightly. On one side between the conchae there is a coagulation of blood without any obvious trace of a mucosal reaction. On the other side an extremely marked exudate is noticed in the sinus, which, after fixation and staining, assumes a more massive and slightly vesicular appearance. In one part the exudate is almost exempt from cells, while in another direction an increasingly pronounced cell reaction is seen with chiefly polynuclear and mononuclear cells in approximately equal proportions, many being in a state of disintegration. In the mucous membrane of the sinus a moderate cellular reaction of mainly a lymphocytic character is observed. The animal 322 shows a still more motley picture. The sinus is on one side covered with an extensive exudate, which centrally consists of an old hemorrhage in the first stage of decomposition. Around it is seen an exudate with an abundance of principally polynuclear cells. In addition the mucous membrane discloses a clearly perceptible inflammatory reaction with plenty of cells, both polynuclear and lymphocytic. To judge from the histological picture, either a bleeding causing an inflammatory irritation has occurred or a hemorrhage of some time ago has been secondarily infected, it being impossible to decide which.

Oxygen deficiency tests, 9—10 volume per cent O_2 at 1 atmosphere.

In this series, embracing the animals 351—363, two display changes, viz., 361 and 362. Here an exudation is found, exactly like that described above from the experiments in the low pressure chamber. 362 reveals a distinct hyperemia, considerably more pronounced than any that occurred in the previously recorded series. No inflammatory changes appear in either of these two cases, whether in the exudation or in the mucous membranes.

Increased oxygen partial pressure, 80—90 volume per cent O_2 at 1 atmosphere.

Of the animals belonging to this group, Nos 401—412, four show histological changes of precisely the same type as those of the preceding tests, except 317 and 322. This applies first of all to 401, 409 and 411. 412 displays, broadly speaking, the same picture, but the edema and hyperemia are in this instance particularly pronounced. Further, the cellular reaction in the exudate is somewhat more marked but mainly lymphocytic. Also in the mucous membrane a slightly increased, chiefly lymphocytic reaction is found. In the latter case the changes are, however, of such a type that the possibility of an infection cannot be eliminated.

Increased oxygen partial pressure in low pressure chamber tests.

This series includes the animals 451—462. In none of these cases are any changes, differing from the control animals, observable.

Control animals.

Changes of the type recorded from the forementioned test series have not been noticed in the control animals. Nor do they in any instance disclose any changes of an inflammatory nature.

Pulmonary changes.

Low pressure chamber tests with normal composition of the atmosphere.

a) Macroscopically, a pronounced increase of the fluid in the serous cavities of the thorax was noticed. Everywhere a bright yellow, watery exudate occurred in varying quantities. As a rule, the lungs disclosed macroscopic changes. They were big, heavy and strongly hemorrhagically stained, showing a distinct increase in consistence. At macroscopic examination the lungs of the animals 311 and 313 disclosed no definite changes.

Microscopically, evident changes appeared in all the fifteen cases except No 313. An intense hyperemia and an alveolar edema

predominates entirely. The lung capillaries display a maximal dilatation. The alveoli seem to be completely surrounded by blood vessels. The alveolar epithelium proper has almost disappeared in the picture (Fig. 40). In addition there are in some instances more or less pronounced hemorrhages in the interstices and in the alveoli. Sometimes the changes appear in spots in the preparation. In other cases pictures suggesting normal conditions are nowhere to be found. As already stated, the edema may contain partly red blood corpuscles, partly, in addition, solitary cells of a monocytic or lymphocytic type. Occasionally, polynuclear cells, often eosinophil, may be noticed. Now and again the edema in the alveoli takes the shape of fibrinous streaks (Fig. 41).

b) Two of the four animals that were killed four days after their last flight did not disclose any definite pathological changes, while two show scattered hemorrhages and minor atelectasis and, in one case, No 317, a partly fairly pronounced hyperemia.

Nos 320—323 display varying pictures of atelectasis, in two instances with a bronchopneumonic picture. No similarity with the pulmonary changes in 311—315 is evident.

Nos 324—327 reveal no distinct pulmonary changes, except the firstmentioned animal which here and there shows a bronchopneumonic infiltration.

In Nos 328—329 there are no definite changes, apart from small subserous petechial hemorrhages, such as may be found in the control animals.

Oxygen deficiency tests, 9—10 volume per cent O_2 at 1 atmosphere.

As in the previous experiments, all cases at macroscopic examination disclosed an increased amount of fluid in the serous cavities of the thorax. The same macroscopic lung changes were noticed in all the instances, except Nos 351 and 352.

Apart from No 352, microscopic examination revealed the same changes, chiefly characterized by hyperemia in the lung capillaries, occasionally combined with hemorrhages and edema (Figs. 42 and 43).

Increased oxygen partial pressure, 80—90 volume per cent O_2 at 1 atmosphere.

In all cases macroscopic examination disclosed an increased amount of fluid in the serous cavities of the thorax. Macroscopically the lungs displayed the same gravely changed, hemorrhagically stained appearance, with one exception, viz., the animal 404, where neither any exudation nor any macroscopic changes were noticed.

At a microscopic examination the picture is, in the first place, characterized by an alveolar edema, often pronounced, and, in addition, a varying hyperemia in the lung capillaries and solitary hemorrhages. More frequently than in the hypoxemia experiments, the edema contains cells of both a lymphocytic and a polynuclear type (Fig. 44). Fundamentally the picture is identical, apart from the fact that the edema is more often more prominent and most conspicuous. The changes are entirely comparable with the oxygen-toxic pulmonary changes described in the literature.

Increased oxygen partial pressure in low pressure chamber tests.

In two cases, viz., Nos 455 and 460, hyperemia is indicated. In addition, these animals, and Nos 451, 452 and 461, disclose minor atelectasis. Otherwise no differences from the control animals are observed.

Control animals.

The control animals disclose no changes of the abovementioned type (Fig. 39). Apart from some minor subserous hemorrhages and solitary signs of atelectasis no pathological changes occur in the animals.

Summary.

The rabbit experiments have produced the following histopathological changes. At a reduction of the prevailing atmospheric pressure with 400 mm Hg in the low pressure chamber, yielding

a partial oxygen pressure of about 70 mm Hg, six hours daily during a period of 10 days, a change characterized by edema, hyperemia, bleeding per diapedesis and transudation will occur in the mucous membrane of the middle ear of rabbit. In 6 out of 15 cases changes, with, approximately, the same histological characteristics, though with a transudation more pronounced than in changes in the middle ear, will appear also in the nasal mucous membrane and the paranasal sinuses. Simultaneously, pulmonary changes will be noticeable, with, on the whole, the same features, viz., edema, hyperemia, in particular, and some hemorrhage. A serous exudation in the thoracic cavities, ascertained at the autopsy, also forms part of the pulmonary picture. The cellular reaction in the mucous membranes, as well as in the exudations, is but faintly pronounced and of such a type that the changes without any doubt can be characterized as non-inflammatory. Fundamentally, animals killed 4, 10, 15 or 20 days after their last flight disclose the same changes in the middle ear in different stages of resorption. In no instance has any sign of infectious inflammatory complication in the middle ear been observed. This does not always apply to the changes in the paranasal sinuses. In two cases, in which the histological pictures reveal hemorrhage and infection, it is impossible to state whether the inflammatory irritation is due to the hemorrhage or to the infection. For as long as 20 days small changes remained in the mucosa of the middle ear, indicating that the regress, though considerable, was not yet entirely complete.

In the second test series the oxygen pressure was reduced to 65—70 mm Hg, 1 atmospheric pressure being maintained. The 13 test animals were exposed to this oxygen deficiency for 6 hours daily during 10 consecutive days. In the mucous membrane in the middle ear, in the nose and the paranasal sinuses (two animals), as well as in the lungs, qualitative and, to some extent, also quantitative changes occurred, of a histological character similar to that of the previously described experiments, where the animals were subjected to a similar oxygen deficiency, though through a reduction of the pressure.

The third test series embraces 12 animals. For 60 hours they were made to breathe 0.8—0.9 atmosphere oxygen.

Also here changes are produced in the mucous membrane of the middle ear, in the nose, the paranasal sinuses and the lungs. The same histological characteristics are noticed also here, with one difference, viz., that the edema is more marked, especially in the lungs.

In the fourth and last test series, comprising 12 animals, the prerequisites have been identical with those of the preceding tests, apart from the fact that the experiments have been performed in a low pressure chamber with the same intermittent reductions in pressure of 400 mm Hg as in the first test series. The partial pressure of the oxygen has in these tests kept at about 0.45 atmosphere. Changes in the middle ear are then insignificant or entirely missing. In the nasal mucous membrane they are totally absent. In the lungs only minor traces of atelectasis, not more pronounced than those noticeable in the control animals, are to be observed.

All control animals of the four test series show altogether normal conditions in the organs that come within the sphere of these experiments. In the lungs only minor subserous hemorrhages are noticed, corresponding to such petechiae as appear at autopsy, and solitary small signs of atelectasis. Such bronchopneumonia as was frequently observed in the animals, during the experiments preceding the forementioned tests, is wholly absent, as a result, no doubt, of the care with which the animals have been selected, with a view to securing a test material free from infections in the upper air passages.

VI.

General discussion

The test material.

Before discussing the results of the tests an analysis of the material of animals employed in the experiments is required. Stress has time and again been laid on the significance of infections of the upper air passages and of otitis media as sources of error. In text books, such as those by Jaffé (1931) and Griffith and Farris (1942), such inflammations are said to be extremely frequent in albino rat and rabbit. However, these authors fail to state clearly that a "clinical" or macroscopic examination will not suffice for the purpose of effectively and reliably eliminating those cases. The importance of a microscopic examination of the nose and the paranasal sinuses, with a view to ascertaining infections, is obvious, as far as the rat is concerned, from the investigations by Keleman and Sargent (1946), as well as from the present one. Both investigations report infections in the upper air passages in 60 and 80 per cent, respectively, of rats which, seemingly, have been in a suitable condition for being confidently used as control animals. The same applies to the middle ear. Nelson and Gowen (1931) noticed spontaneous otitis media in 40—50 per cent of rats of such an age as those employed in the present investigation, a figure which well conforms with that of the present material, viz., 43 per cent.

Thus, the white rat is badly suited for experiments of the present kind. In view of the fact, however, that in American quarters this particular animal has been recommended as fit for standard experiments, an object which it will not serve, at least not in connection with experiments such as the present ones, a fairly thorough report has, nevertheless, been given of

these tests. The histo-pathological picture issuing from these experiments on rats, as compared with those on rabbits, provides a rather striking example of the immediately misleading results which infections in the upper air passages in the test animals are apt to cause.

As far as the rabbit is concerned the position is somewhat different. A material of animals free from such infections may in this instance be secured, provided that the attention is properly directed towards the risks connected with infections of the upper air passages, that the investigator possesses some experience in clinically judging the animals, that he carries out his examination carefully, before the animals are brought to the tests and, further, that a quarantine be imposed upon the animals. In addition, in the present material a histological examination of the rabbits, for the control of the nose and the paranasal sinuses, has without exception been performed, similar to the procedure adopted in the rat experiments. In no instance have any pathological middle ear or nasal changes been observed in the control animals. This histological control should provide a more reliable and objective guarantee than any clinical examination can furnish, viz., that the animals are exempt from infections in the organs to be studied. This high standard of the present test material is evident also when regarded from another point of view. According to a statement in JAFFÉ's forementioned text book bronchopneumonia frequently occurs in the rabbit. In the experiments preceding the tests, changes of such a nature were in several instances observed, but in the control material of the definitive experiments no changes whatever of that kind appeared, which may not be without connection with the fact that these animals were exempt from infections in the upper air passages. Moreover, the changes in the test animals are of a different character.

Thus, dissection through the nose and the paranasal sinuses affords an opportunity of establishing a fairly reliable control of the material of animals, both rat and rabbit, from the point of view of infections of the upper air passages. As far as the rat is concerned ordinary macroscopic examination cannot be substituted for this method of control, which, because of its greater objectivity and its superior reliability as against clinical examin-

ations, should prove useful also with regard to other kinds of test animals, as well as on occasions when other problems have to be solved.

With this in mind an analysis of changes ascertained in the middle ears in the present experiments on rats should be appropriate. They are inflammatory with a genuinely purulent exudation and can only be termed otitis media purulenta. On account of the spontaneous infections of the animal material they can by no means justify any conclusions serviceable for the problems under discussion here. It is of interest, of course, that the changes have proved more pronounced in the test animals than in the control animals. In this instance the mechanism is probably as follows. The open tube fulfils no flutter-valve function. Thus, at variations in pressure pus can be drawn through the tube. In spite of the temporary drainage which this withdrawal of discharge implies, each experiment will probably end by adding mostly infectious secretion drawn up from the naso-pharynx into the middle ear. The patho-physiological mechanism thus widely differs from that which is supposed to apply to Man.

In this connection a particular observation should be emphasized. Notwithstanding the great number of cases of otitis, in the entire material of rats not a single instance of suppuration out into the auditory canal has been noticed, whether macroscopically or microscopically, while, in the experiments preceding the definite tests, rabbits with spontaneous otitis disclosed such suppuration with considerable perforation on the tympanic membrane. In the opinion of the present author, the differences in the tubal function may here serve as an explanation. As far as the rats are concerned, the permanently open tube will, even in the case of grave inflammations, provide a drainage from the naso-pharynx. This does not apply to the rabbit, the tube of which functions in a way similar to that in Man. This fact, hitherto unrecorded in the literature, again confirms the difference in the tubal function in rat and rabbit which has been ascertained anatomically by the development of m. tensor veli palatini as well as experimentally in low pressure chamber.

To what extent are oxygen deficiency and oxygen poisoning tests on animals applicable to the human organism?

In the present work both clinical-physiological investigations on Man and experiments on animals are reported. Though fundamentally greatly differing, investigations suggest a certain parallelism, which brings into notice the standing, and always difficult, problem in connection with experimental inquiries, viz., to what extent the results gained will permit conclusions with regard to Man. The difficulties of drawing such parallels are inherent in all experimental investigations but, nevertheless, continue to defy all attempts to place them in a clear perspective. On the other hand, as the problems of this investigation have been formulated, histo-pathological studies which are of particular interest, not least from a practical clinical point of view, can in this case be carried out only by means of experiments on animals.

According to several data in the literature, the human organism appears to be more sensitive to oxygen deficiency than our ordinary experimental animals (Bert, 1878, Armstrong, 1943, Ruff and Strughold, 1944). The reduction in pressure of 400 mm Hg applied in the present experiments, corresponding to an altitude of about 6000 m (18 300 feet) might, with the comparatively long time of exposition, viz., 6 hours, prove fatal to Man, while the test animals easily endure an oxygen deficiency of such an altitude. This has been further illustrated by such studies of organic changes, owing to oxygen deficiency, in the central nervous system, liver, cardiac musculature and lungs, as have been carried out by Luft (1937), Büchner (1941) and his collaborators and Pischotka (1942). The animals have come alive through such reductions in pressure as have been used, viz., corresponding to altitudes of 10 000 m (30 500 feet) or more. With the length of exposition which the experiments have involved the human organism would probably not have been able to survive.

As far as oxygen poisoning is concerned the position becomes to a certain extent reversed. Small test animals, such as guinea-pigs, rats and rabbits, die after about 3 days' exposition to 0.7—1.0 atmosphere oxygen, while monkeys and dogs endure much better (Clamann and Becker-Freyseng, 1940, Liebegott, 1941,

Friedreich and Grayzel, 1944). The same authors emphasize also the wide range of individual variations within one and the same species, a fact noted in various physiological connections also in the case of oxygen deficiency (Armstrong, 1943, Ruff and Strughold, 1944). Investigations by Comore et al. (1945), Reinhard et al. (1943) and Ohlsson (1947) show that, as far as increased oxygen pressures are concerned, the human organism is far more resistent than certain test animals, such as, for instance, rat and rabbit.

Since, however, in the present instance qualitative comparisons alone are taken into account and a conspicuous parallelism between various clinical results and morphological findings from experiments on animals is noticeable, e.g., reduction in vital capacity in oxygen deficiency and oxygen poisoning, and corresponding histo-pathological findings, and since, further, the experimental observations on rabbits in this investigation may constitute an acceptable answer to the questions under discussion, an application of the results arrived at to the human organism seems well justified.

The histo-pathological results of the experiments on rabbits and their applicability to the problem.

Armstrong and Heim (1937) base their account of the patho-anatomy of aero-otitis media on clinical observations, otoscopic findings and on the patho-physiological mechanism presupposed by them, as by Fretzel (1939) and their later followers. Reductions in pressure in the middle ear would cause a passive hyperemia, while increases in pressure would result in an ischemia, followed later by a reactive hyperemia. This would in due course lead to a "traumatic inflammation" with mucosal swelling. The mucosal epithelium would share in the reaction. Then, hemorrhages and hydrops ex vacuo into the tympanic cavity would appear. The results from low pressure chamber tests with a normal composition of the atmosphere offer certain similarities with this theoretically outlined patho-anatomical picture, but also essential divergencies. Microscopic examination discloses edema, hyperemia, hemorrhages and transudation.

To judge from the histological pictures, a circulation disturbance with changes in the vascular permeability in the mucous membrane of the middle ear would be the primary factor. The fact that the same changes are obtained by a decrease or an increase in the oxygen pressure without any difference in the atmospheric pressure constitutes a direct denial of "a cupping effect", such as Armstrong and Heim and their successors have described. The term "a traumatic inflammation" which they use cannot be called appropriate, partly for the forementioned reason, partly because the inflammatory feature of the picture is too inconsiderable to be interpreted as anything but a reaction against the previously described changes, and even then it is so faintly pronounced as to render the term inflammation misleading.

As to the changes in the nose and the paranasal sinuses the position is identical. Gurkow (1940) defines the mucosal changes in the paranasal sinuses, observed experimentally, as "Blutergiessungen in den Schleimhaut, Unterschleimhaut und tiefer liegende Geweben. Ausserdem Erweiterung der lymfatischen Spalten in den Schleimhauthüllen und Unterschleimhautgeweben." He pays no attention to the possibility of infection. However, to judge from his micro-photos, this possibility seems far from being excluded, an interesting fact, in view, not least, of the difficulties that have been met with, in this respect, in the present investigation. Gurkov quotes an investigation by Magnotti (1936), unavailable here. Campbell's (1945) division into obstructive and non-obstructive aerosinusitis is based on clinical observations and on one single animal experiment. The histological picture in the present investigation, considered in connection with the fact that the same changes have appeared in all the experiments where the oxygen pressures have been altered, places the matter in a different light. A mucosal swelling due to edema and hyperemia occurs but this affects all the mucous membranes in the nose as well as in the paranasal sinuses and, in several instances, identical changes are noticeable both in the paranasal sinuses and the nose. Nor do the hemorrhages occupy the dominating position ascribed to them by Campbell and Gurkow. The mucosal swelling, noticed in the present investigation, may, of course, produce an obturation of the

sinusal ostium but, should the changes originate in this obturation, the exudate would appear only distally from the obstruction in the paranasal sinuses and not in the nose. However, even then the mucosal swelling originating in the oxygen deficiency, and not in the change in the gas volume, becomes the causative factor. In two cases in the present material a study of the resorption has revealed histological signs of an infection, combined with an older hemorrhage. Whether this is reactive to the hemorrhage, or is due to an infection, cannot be decided. However, it may be borne in mind that the nose normally contains a bacterial flora which, secondarily, can establish itself in the mucous membrane damaged by a barotrauma, i.e. oxygen deficiency, or an increased oxygen pressure. These experiments seem to suggest that the primary factor, as far as the rabbit is concerned, is to be found in the changes in the oxygen pressure, when increased or decreased beyond certain physiologically tolerable limits, and not in the differences in the gas volumes subsequent to the changed pressures.

Supposing Armstrong's and Heim's and Frentzel's arguments were altogether accepted, distinct similarities should occur between the patho-anatomical picture of otosalpingitis and that of aero-otitis media. The patho-anatomy of otosalpingitis is known only from a relatively small number of experimental investigations. Lennart Holmgren (1940) has, inter alias, microscopically examined the mucous membrane in the middle ear in dogs in which the pharyngotympanic tube has been ligated. 6 of 10 animals did not display any mucosal changes, while 4 showed signs of subacute or chronic inflammation of the mucous membrane in the middle ear. To judge from that investigation, the patho-anatomy in aero-otitis media and otosalpingitis, respectively, does not disclose any very obvious similarities.

How, then, will this theory conform with earlier statements? As far as experiments on Man with oxygen deficiency and a maintained atmospheric pressure are concerned no data have been available for the purpose of the present investigation. The existing great variety of physiological experiments with oxygen deficiency on Man have throughout served wholly different aims, and it seems fairly natural that the multiplicity of conspicuous

symptoms appearing in these experiments have altogether overshadowed such ear troubles as may have occurred. With regard to oxygen poisoning with a maintained atmospheric pressure data are comparatively frequent. Reinhard et al. (1943), Comore et al. (1945) and Ohlsson (1947) state that their test persons noticed troubles in the upper air passages, including the nose, as well as in the middle ears, Ohlsson adding also in the sinuses. All these instances concern increased partial oxygen pressure at 1 atmosphere. Moreover, the troubles have without exception set in while the experiments were proceeding. This will have to be remembered also with regard to the ear troubles in aviators, who have breathed high oxygen concentrations from the beginning to the end of a flight, including the landing, i.e. the socalled oxy-otitis media, described by Behnke (1945). About 18 hours after the end of the flight the pilots noticed subjective ear troubles which were objectively verified as dropsy in the middle ear. After a few days these troubles disappeared, both subjectively and objectively, without any therapeutics. Behnke suggests the term of oxy-otitis and points to a high oxygen concentration in the air in the middle ear after a flight as the genesis. Later an oxygen resorption would, in his opinion, take place with a consequent hydrops ex vacuo. Whether or not the observed changes would be due to oxygen poisoning is a question which he does not enter into. Also, as to the ear troubles in compressed air workers an increase in oxygen pressure will have to be taken into account. When total pressures of more than 3 atmospheres are reached, the oxygen pressure increases to such an extent as to exceed the physiologically tolerable limit of about 500 mm Hg. This is exactly what happened in an earlier investigation. Rips (1939) describes changes, obviously identical with those occurring in the present investigation, in the middle ears in animals subjected for several consecutive days to pressures of 3—4 atmospheres, to be followed by a slow decompression back to atmospheric pressure. Still, Rip's experiments are not altogether commensurable with the present ones, since, in his instance, changes caused by diver's disease have to be taken into consideration, a fact that has to be kept in mind with regard to Rip's as well as Vail's experiments.

In so far as more extensive reports are concerned, clinical investigations regarding aero-otitis media, its morbidity, the risk of complications, etc., mostly refer to low pressure chamber tests, owing supposedly, in the first place to the superior control facilities, and the availability of specialists, at the experimental stations for aeromedicine, where these tests have been performed. However, one factor may probably played a not immaterial part in this connection. The principal purpose of the low pressure chamber tests with aviators has been to provide the test persons with a practical demonstration of the dangers of oxygen deficiency, such as may be met with when flying. Thus the majority of low pressure chamber tests aim at producing in a crew of an aeroplane an oxygen deficiency which may be more pronounced than they will usually be exposed to in actual flying, where the risks are greater and the consequent considerations of safety rules will not allow practical demonstrations. If, in addition, experiments with high oxygen concentrations are performed, perhaps in immediate connection with the previous ones, and, may be, inhaled at a non-reduced pressure, an increased likelihood of a traumatism through changed oxygen pressures will occur.

With the reservations previously stated, concerning the applicability of results from experiments on animals to the human organism, the questions formulated in the present investigation may to some extent be answered.

Different variations in pressure may produce mucosal symptoms in the middle ears, the nose and the paranasal sinuses, as soon as any changes in pressure entail oxygen pressures beyond physiologically tolerable limits. As long as the mucosal swelling does not obturate the respective ostia, or transudation does not occur, mucosal changes may, conceivably, appear without any such subjective symptoms as will clinically justify a diagnosis of aero-otitis media and aerosinusitis also in Man. Clinically several authors, Dickson et al. 1944, Stewart et al., 1945, Lieberman, 1946, have found otoscopic changes without any subjective troubles. In connection with such clinical findings there has probably been corresponding mucosal changes of the type indicated above. Mucosal changes of a similar nature may also be found in the

nose and the paranasal sinuses and may then cause a wrong diagnosis. An apparent rhinitis is not necessarily of an infective nature. The genesis may have to be looked for in mucosal changes originating in changed oxygen pressures. Should the changes in the middle ear have reached such a point as to manifest themselves as an aero-otitis media, there is reason to expect a more marked mucosal swelling and a more prolonged mucosal restitution, retarded partly through the anatomical conditions governing the vascular drainage of the mucous membrane of the middle ear. The experiments regarding mucosal restitution speak in favour of this contention. In the experiments on animals it remained incomplete after as long as twenty days. Likewise, the morphologically ascertained pulmonary changes may probably in a clinical way be ascribed to similar diagnoses. As far as oxygen poisoning is concerned, this has, in fact, clinically been shown to be exceedingly likely, e. g., bronchitis Clamann & Becker-Freyseng (1939), nasal congestion or coryza, Reinhard et al. (1943), Comore et al. (1945), sinusitis Ohlsson (1947). Galloway (1946) describes similar clinical symptoms in the air passages in the event of oxygen deficiency, stressing the fact that an obvious parallelism is often to be found with the symptoms in anoxia, due to abnormalities of a different origin in the respiratory tract, and such as aviators sometimes display at high altitudes.

However, to our knowledge the test animals do not disclose anatomical variations in the nasopharynx and, e.g., the nose to such an extent as will daily be found in Man, a factor speaking against a direct application of the experimental results from the present investigation on Man. For this reason, aero-otitis media and aerosinusitis in Man will not be concluded to be due alone to changes in oxygen pressures. On the other hand, the results of the present investigation appear to suggest that the mechanical explanation previously referred to does not exhaust the matter, but that a new factor, which probably is patho-genetically significant, has been ascertained.

The histo-pathological findings as part phenomena in general patho-physiological processes due to oxygen deficiency and oxygen poisoning.

From earlier literature pulmonary changes, originating in oxygen deficiency and oxygen poisoning, are known, through physiological as well as morphological observations.

Hypoxia causes increased ventilation and expelling of carbon dioxide. The significance of the oxygen partial pressure with regard to the respiration and its regulation, and all the questions arising in this connection, have to a large extent attracted the attention of the physiologists. This comprehensive problem will not be dealt with here; an extensive material has been produced by Bjurstedt (1946). However, the hypoxia implies a reduction in vital capacity, an interesting point in this connection. As early as in 1878 Paul Bert reported this observation. Later several authors have confirmed it, among others Mosso (1889), Zuntz et al. (1906), Grollman (1930), Schubert (1930), Schneider (1932) and Perl (1939). Earlier, different theories have been propounded about the genesis of this reduction in vital capacity. In the opinion of Zuntz (1906), it originates in an increase of the intestinal gases, owing to a decrease in pressure, forcing the diaphragm upwards with a consequent reduction in vital capacity. Fuchs (1908) looked for an explanation in the lower temperatures prevailing at high altitudes. This would, he suggested, result in a generally increased muscle tonus with ventilation difficulties. As early as 1906 Bohr thought he would find the cause in a decrease in the oxygen pressure. Through low pressure chamber experiments and, also, from observations made during an expedition to Pike's Peak (14 110 feet), Schneider (1932) could ascertain a reduction in the vital capacity which could be counteracted by the administration of oxygen. It was mostly not noticed until at an altitude of 12—14 000 feet. No expansion of the abdominal volume could be found. Nor did the temperature play any noticeable part. Schneider's conclusions, i.e. that "the reduction in vital capacity is due to an engorgement of pulmonary vessels, that reserve capillary paths are brought into requisition and that possibly there is a relaxation

of pulmonary capillaries as a result of anoxemia," correspond probably better with current contentions than any previous statement. Anthony (1937) and, later, Armstrong (1943) have noted the same reduction in vital capacity and its elimination by means of an increase in oxygen pressure. This purely physiological observation has been quoted as an illustration of the histological pulmonary changes obtained both in section material in Man and by experiments with rabbits.

Müller and Rotter (1942) performed an autoptic examination of four aviators who died in aeroplane accidents at high altitudes from acute oxygen deficiency. Macroscopical examination disclosed in all cases an intense hyperemia and, in three instances, a pulmonary edema. Microscopically all cases showed an intense congestion in the pulmonary capillaries and a pronounced pulmonary edema.

As regards organic changes owing to oxygen deficiency the literature offers many data, inter alia concerning the central nervous system, liver, heart musculature and kidneys. As far as the lungs are concerned available data are, however, much more sparse, appearing only in passing, in connection with information on other matters which form the main theme. Armstrong and Heim (1938) exposed 16 rabbits to daily pressure reductions, corresponding to altitudes of 6000 m, (19 650 feet) finding pulmonary changes in the form of hyperemia, hemorrhages and edema. Luft (1938) defines the changes he observed as stasis with a partial edema. Miller (1944) subjected 12 sheep to pressure reductions, corresponding to heights of 31 000—46 000 feet, finding, inter alia, in 10 cases a pronounced transudation in the pleurae and pericardium with transudation amounting to 60—500 cc. No data regarding the condition of the lungs themselves are given.

In sum, in Man, as well as in test animals, uniform autoptic findings, viz., an intense congestion, edema and, in addition, often a hemorrhage and dropsy in the serous cavities of the thorax, correspond with the clinical observation of a reduction of vital capacity owing to oxygen deficiency. As a matter of fact, the forementioned changes should all contribute towards reducing the vital capacity.

The literature regarding the physiological effect of oxygen over-pressure, and the consequent pulmonary changes, is extremely extensive. In recent years several authors have offered excellent surveys of works on the subject, Ohlsson (1947), and Troell (1947). A brief resumé will, therefore, suffice here. Those who want further details will find them in the forementioned works.

In connection with the investigations published by Paul Bert (1878), Smith (1899) performed experiments on animals of different kinds. He showed that, within 24 hours or longer, oxygen concentrations of 80—96 volume per cent at 1 atmosphere caused pronounced lung changes, characterized by hyperemia, edema, degeneration and desquamation of the alveolar epithelium. By longer exposition he obtained a more pneumonic picture, probably of an irritative origin. When the pressure increased, the changes appeared sooner and led more rapidly to death. These investigations have later been verified by a number of scientists. Both Schmiedehausen (1909) and David (1912) used rabbits. They found these animals extremely sensitive to high oxygen pressures. Investigations by Karsner (1916), Binger et al. (1927), Boothby (1932) and Campbell and Poulton (1934) confirmed that the oxygen concentration, in order to produce these changes, must, at 1 atmosphere, be about 70 volume per cent or more. Armstrong (1938) made rabbits breathe 90 volume per cent at different pressures. At 0 feet the animals died after 84 hours, at pressure reductions corresponding to 5000 feet after 156 hours and at 10 000 feet after 215 hours, some of the animals survived. At altitudes of 20 000—30 000 feet they began to disclose signs of oxygen deficiency. At 47 500 feet they died after 7 minutes, at 50 000 feet after 3 minutes. Binger (1927) and later Clamann et al. (1940) emphasize the non-inflammatory picture which is defined as a pronounced hyperemia in the lung capillaries with interstitial edema, alveolar edema, desquamation of the alveolar epithelium and a moderate cell infiltration. Microscopic and bacterial examination, performed by the forementioned and other scientists, have provided no support for any inflammatory genesis, even though the final stages have produced a pneumonic picture. Furthermore, the

macroscopic picture is supplemented by transudation in the serous cavities in the thorax, experimentally observed by Pflesser (1937), Pischotka (1941) and Liebegott (1941) among others.

While a great many scientists have carried out experiments on animals, those in Man are less numerous. Clamann and Becker-Freyseng (1939) performed experiments on themselves. For 65 hours they breathed 90 volume per cent oxygen at 1 atmosphere. Apart from a reduction in vital capacity they noticed subjective troubles in the form of bronchitis, involving a week at a hospital for one of them. A similar reduction in vital capacity had been ascertained as early as in 1932 by Katz et al. Identical observations have later been made by Comore et al. (1945) and Ohlsson (1947). A different opinion is held by Boothby et al. (1939), Evans (1944) among others, but against their conclusions the objection can be made that the gas administration has taken place through a respiratory mask, viz., the BLM mask, which, according to later investigators, implies a risk of leakage etc. Sakland and Burgers (1944), at control experiments with the BLM mask, ascertained variations in oxygen concentrations between 40 and 95 volume per cent. Clamann and Becker-Freyseng (1939) ascribed the loss in vital capacity to the pulmonary changes recorded in the animal experiments. In experiments on human subjects no author has been in a position to find any pulmonary changes by röntgenological examination.

The subjective symptoms in the upper air passages, paranasal sinuses and the middle ears, mentioned as additional findings in oxygen poisoning experiments on Man, attract a particular interest in this connection. In view of their intimate connection with the forementioned works they will be referred to here. Reinhard, Moore, Dubach and Wade (1943) subjected four patients, suffering from sickle cell anemia, to 0.8—1 atmosphere oxygen over a period of 8—20 days. The exposition was not absolutely continuous. The patients breathed, while eating, through a mask over the nose, which probably caused a considerable reduction in the oxygen pressure. However, the patients revealed certain symptoms which the authors characterize as no

distinct toxic symptoms but which nevertheless, can hardly be interpreted as anything but effects of oxygen poisoning, i.e. signs of inflammation of the mucous membrane and congestion of the upper respiratory tracts, increased nasal secretion and deteriorated hearing. Comore et al. (1945) had at their disposal a relatively large material of young men. 43 per cent of those who breathed pure oxygen had nasal congestion or coryza during the tests or immediately afterwards, 25 per cent had ear troubles. Three of Ohlsson's (1947) six test persons, who breathed about 0.8 atmosphere oxygen for approximately 60 hours, developed symptoms in the nasal cavities and, in two instances, also complained of ear troubles. One had transudation in the middle ear, the other showed a dense opacity of the paranasal sinuses röntgenologically which he considers to be an oxygen toxic effect.

In the experiments on rabbits in the present inquiry macroscopic examinations have revealed pulmonary changes of the same character, combined with exudations in the serous cavities, due to increased as well as decreased oxygen pressures. Also, the microscopic picture is found to be rather uniform, characterized, in the first place, by hyperemia and an alveolar edema, sometimes together with small hemorrhages. Even though the histological picture may vary fairly considerably, having in mind the wide differences between the organs concerned, the same qualitative histological characteristics will be noticed in the pulmonary changes, in the event of variations in the oxygen pressures, as those appearing in the mucous membrane of the middle ear, the nose and the paranasal sinuses. Clinical data are available regarding troubles in the ears and the sinuses, caused by increased oxygen pressures at a maintained atmospheric pressure (Reinhard et al., 1943, Comore et al., 1945, Ohlsson 1947) or through an increased atmospheric pressure (Vail, 1929, Behnke, 1934 and 1945, Requarth, 1941) and a consequent increase in oxygen pressure.

As regards oxygen deficiency data are limited to aero-otitis and aerosinusitis observed in connection with reductions in pressure. Apparently, here is a blank in our knowledge which the present investigation may to some extent fill up, viz., ear changes in the case of oxygen deficiency at maintained atmospheric

pressure, after which the parallelism existing between, on the one hand, pulmonary changes and, on the other, changes in the ear, the nose and the paranasal sinuses — also in this instance with a changed oxygen pressure — would be explained. As far as the paranasal sinuses are concerned Gurkow (1940) seems to have ascertained changes similar to those described in this investigation. However, the micro-photos he has published lack clearness and, at least partly, they indicate infections.

The reduction in vital capacity — clinical ear symptoms due to increased or decreased oxygen pressures, in the former event also at maintained atmospheric pressure — and the histo-pathological pulmonary changes known from earlier experiments, all these factors would, together with the changes observed in the present investigation, in the lungs and middle ears as well as in the nose and paranasal sinuses, with the same qualitative characteristics, originating in changed oxygen pressures, and not in any changes in the total pressure, speak in favour of a contention that *the noticed changes are not to be regarded as local but may, in the first place, be interpreted as part phenomena in a general reaction of the organism to changed oxygen pressures, whether increased or decreased beyond physiologically tolerable limits.*

As far as oxygen deficiency is concerned, such a supposition of general physiological processes finds support in such histopathological, degenerative organic changes, in the central nervous system, liver, kidneys and heart musculature, as have been ascertained by Luft (1938), Büchner (1941), Pischotka (1942) and others. Clinically ECG-changes in the case of oxygen deficiency are known Rühl (1938), Rühl et al. (1938), Leedhem (1939), Schütz (1941), and others. Also in oxygen poisoning ECG-changes have been observed — Kümmel (1938), Anthony and Kümmel (1939), and Barach and Steiner (1940). In addition, Kühn, in the course of experiments on rabbits and guinea-pigs, has noted ECG-changes together with extensive anatomical changes in the cardiac muscles, described as being of the type found in oxygen deficiency, Liebegott (1941), Kühn (1944). Furthermore, both Liebegott (1941) and Pischotka (1941) have ascertained in the liver cells a vacuolar degeneration which, in the opinion of Liebegott (1941), conforms with findings in the case of oxygen

deficiency. Troell (1947) has experimentally demonstrated that intestinal motility is retarded in the event of oxygen poisoning. Weltz and v. Werz (1942) have shown, both in vivo and in isolated intestinal preparations, that the same happens in connection with oxygen deficiency. Microscopic changes in the central nervous system of test animals, in connection with oxygen poisoning, have been ascertained by Bean (1945), histo-pathologically characterized as congestion, perivascular edema, as well as edema in focal areas of anemic necroses in the white substance. Luft (1938), Büchner (1941), Morrison (1946), among others, describe similar changes at oxygen deficiency.

From the observations recorded in the literature the parallelism between the findings in the case of oxygen deficiency and oxygen poisoning is so conspicuous as to provide, it will appear, a further confirmation of the suppositions submitted in the present inquiry. Moreover, since the changes occur in so widely different organs, it will, in the instance of oxygen deficiency as well as of oxygen poisoning, seem unlikely that they should manifest a local irritative effect, of changed oxygen pressures, restricted to a certain organ. The observation made in the present investigation that both oxygen deficiency and oxygen poisoning reveal themselves through the same morphological characteristics in the mucous membranes of the middle ear, the nose and the paranasal sinuses will, perhaps, at first, seem surprising, considering that the two physiological mechanisms that are concerned may to some extent be regarded as mutually opposite. From the above quotations from the literature it is, however, evident that the same applies to a whole series of morphological as well as clinically physiological observations. In fact, the results arrived at in the present investigation well conform to those of earlier ones, thus supplementing our knowledge of the patho-anatomy of oxygen deficiency and oxygen poisoning.

It is interesting to note in this connection also the patho-physiological genesis of the morphological findings, indicated by Pischotka (1941), Liebegott (1941) and Kühn (1944), viz., that the oxygen poisoning would result in such a grave injury to the alveolar epithelium, "Quellungsnekrosen", as to cause the appearance of a "hypoxemia". Be this as it may, the question

cannot be answered by means of any purely morphological studies but has to be left open for the present. Furthermore, it lies beyond the scope of this investigation. However, the opportunities that offer themselves for further research in this field, by combining physiological and morphological investigations, should be stressed.

VII.

Results and conclusions

1. Low pressure chamber experiments on rabbits produced in the mucous membranes of the middle ear, the nose and the paranasal sinuses non-infective circulation disturbances, histopathologically characterized by edema, hyperemia, bleeding per diapedesis and transudation. Oxygen pressure about 70 mm Hg.

2. When rabbits were exposed to an oxygen deficiency of about 9—10 volume per cent or to oxygen poisoning of about 80—90 volume per cent at 1 atmosphere, qualitatively uniform changes appeared in the respective mucous membranes. Oxygen pressure 65—70 mm Hg and 0.8—0.9 atm.

3. Oxygen poisoning tests, combined with reductions in pressure in a low pressure chamber (as in paragraph 1) produced either no mucosal changes at all or exceedingly slight ones. Oxygen pressure about 0.45 atm.

4. Consequently, the etiologically essential fact, with regard to the occurrence of mucosal changes in these experiments on rabbits, has been the reduced or increased oxygen partial pressures.

5. In the test series with considerable changes in the oxygen pressure the animals disclosed an exudation in the serous cavities of the thorax and histological pulmonary changes of the same characteristics as the previously mentioned mucosal changes. From this it is probable that the observed changes are not to be regarded as isolated local changes but should be looked upon as part phenomena in general physiological processes.

6. The observation that oxygen deficiency will produce histopathological changes in the middle ear, the nose and the paranasal sinuses, similar to those originating in oxygen poisoning, conforms well to a series of clinical and histo-pathological observations in animals as well as Man.

7. With the reservations regulating the applicability of test results from experiments on animals to Man, these results may answer the questions on page 18, which are based on clinical observations. Aero-otitis media and aerosinusitis would histopathologically appear as described in paragraph 1. The uniform pathological picture, both in the event of increased and decreased oxygen pressures, may explain the similar clinical picture in different forms of barotrauma, whether it has resulted in an increased or a reduced oxygen pressure, or pure oxygen has been inhaled. Clinical symptoms will probably appear only when the mucosal changes have manifested themselves in transudation or obturation of the respective ostia. The fact that the changes are non-infectious may account for the insignificance of the risk of suppurative inflammations. The mucosal changes also affect the nasal mucous membrane, being of such a nature as to cause them to be clinically misinterpreted as infectious. Therapeutics, with a view to counteracting the pressure, have no effect upon already existing mucosal changes, and, owing to the special conditions of drainage in the middle ear, the mucosal restitution, and consequently also the disease, may, in spite of any therapeutic intervention, be prolonged over several weeks.

VIII.

General summary

Part II contains a survey of the literature on aero-otitis media and aerosinusitis. Earlier experimental investigations on these subjects, which are relatively sparse, are dealt with one by one. On the basis of this account of the clinical literature the questions to be discussed in the present inquiry are set forth, while stress is, at the same time, laid on the fact that an investigation of this kind has to be carried out exclusively by means of experiments, in order to give morphological data.

The purpose of the investigation (Part III) has been to produce, by means of experiments on animals, changes in the mucous membrane of the tympanic cavity and the paranasal sinuses under such conditions as would, conceivably, conform to the clinical conceptions of aero-otitis media and aerosinusitis. Histo-pathological examinations of the test animals have been performed with a view to establishing the morphological basis of the forementioned clinical conceptions. Through uniform histological analyses an attempt has also been made to shed light on certain clinical observations, which are left unexplained by the generally accepted genesis, viz., the flutter-valve function of the pharyngotympanic tube through changes in pressure. The particular questions to be answered are as follows: 1) Why do different forms of barotrauma produce uniform clinical pictures? 2) Why do objective ear findings sometimes occur without any subjective troubles? And 3) Why is the risk of complication with suppurative inflammation so insignificant?

Part IV begins with a description of apparatus and methods. In the first place an account is given of the low pressure chamber which was built for the present purposes.

The first tests in the low pressure chamber were carried out on white rats. The occurrence of infections in the upper air pas-

sages and of otitis media in the control animals, in 87 and 43 per cent, respectively, renders the rat less well suited to experiments of this kind. Particular attention was paid to the question whether these animals, clinically and macroscopically, appeared to be in such a trim as to be confidently used as test animals. The forementioned infections were ascertained only at microscopic examination. The patho-anatomical changes in the control as well as test animals were inflammatory. By measuring the mucosal thickness, and the thickness of the tympanic membrane in the middle ear, and by a subjective estimation of the character of the exudation and, further, through a statistical analysis of the material, the reductions in pressure to which the test animals have been exposed are shown to exert, in all likelihood, a certain amount of influence on the degree of the inflammation, being less pronounced when oxygen was added. The inflammatory character of the changes, as well as the fact that the pharyngotympanic tube in rat is permanently open, prevent the drawing of any conclusions from these tests with regard to Man. The method worked out for the purpose of the control of infections and, further, the observation that the oxygen pressure probably affected the degree of the changes have determined the procedure in the later tests.

In Part V the experiments on rabbits are described. It is pointed out that the function of the pharyngotympanic tube in rabbit is of the same flutter-valve type as in Man. Clinical, macroscopic as well as microscopic, examinations of the rabbits definitely suggest the probability that the control as well as the test animals used in the definitive experiments have been exempt from inflammatory changes in the organs concerned. Tests in the low pressure chamber produced in rabbit mucosal changes of a non-inflammatory type in the middle ear, the nose and the paranasal sinuses. Histo-pathologically the changes were characterized by edema, hyperemia, bleeding per diapedesis and transudation in the respective cavities. Oxygen deficiency of 9—10 volume per cent yielding approximately the same oxygen pressure as in the previous tests, produced qualitatively similar changes. Oxygen poisoning, at 0.8—0.9 atmosphere of oxygen, produced in the forementioned organs also histo-pathologically

the same mucosal changes. The poisoning effect of oxygen could be eliminated by reduction of the atmospheric pressure with 400 mm Hg as in the experiment in low pressure chamber.

Part VI comprises a general discussion of the results. The importance of a reliable control of the test material from the point of view of infections is again emphasized, particularly the significance of a microscopic examination of the nose and the paranasal sinuses.

The difficulties generally attending an application to Man of results from experiments on animals are indicated. Nevertheless, there is justification here for assuming similar conditions to prevail. This offers the only way to gain an idea of the morphological changes in aero-otitis media and aerosinusitis in Man. The results thus obtained can be accepted as a probable explanation of certain clinically unelucidated problems. In view of the fact that earlier experimental and clinical observations, in the case of oxygen deficiency and oxygen poisoning, have often been found to conform well, there seems to be further justification for applying the experimental results of the present investigation to Man.

Certain data in the literature induced an examination also of the lungs. In a survey of the literature on oxygen deficiency and oxygen poisoning clinical physiological observations are recorded of, inter alia, reductions in vital capacity in the case of oxygen deficiency and oxygen poisoning, as well as of patho-anatomical investigations which provide a morphological background for these findings. In this connection an account is submitted also of aero-otitis media and of symptoms indicating aerosinusitis in the case of oxygen poisoning. In all cases where oxygen deficiency or oxygen poisoning had occurred histopathological examinations of the lungs of the test animals disclosed changes of a non-inflammatory nature, with the same qualitative characteristics as mentioned above. No particularly marked difference in the pulmonary changes in oxygen deficiency and oxygen poisoning, respectively, could be ascertained.

Considering the fact that changed oxygen pressure at 1 atmosphere of total gas pressure produces the same qualitative histopathological changes, it should be obvious from the present

test results that the "mechanical" genesis of aero-otitis media and aerosinusitis fails to cover the whole truth. In experiments the flutter-valve function of the tube has been eliminated. Also clinical observations, e.g., concerning symptoms in the middle ear and upper air passages in the case of oxygen poisoning, point in the same direction. This latter fact, together with experimental findings in the lungs, the central nervous system, the cardiac musculature, the liver and the kidneys, and, further, a great number of clinical observations suggest that *the experimentally observed changes in the present investigation should, in the first place, be regarded as part phenomena in general physiological processes caused by oxygen deficiency and oxygen poisoning.* Applied to Man, this theory would, inter alia, explain why different forms of "barotrauma" produce identical clinical pictures, why, further, otoscopic changes may be found without any clinical symptoms and, finally, why the risk of complication with suppurative inflammations is practically non-existent.

It is a particularly interesting fact that oxygen deficiency as well as oxygen poisoning have manifested themselves in a similar way in the mucous membranes of the middle ear, the nose and the paranasal sinuses, bearing in mind, first and foremost, that a great many instances in the literature confirm that these two physiological processes have led to the same morphological and clinical manifestations.

IX.

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X.

Micro-photos

Micro-photos of preparations from rats.

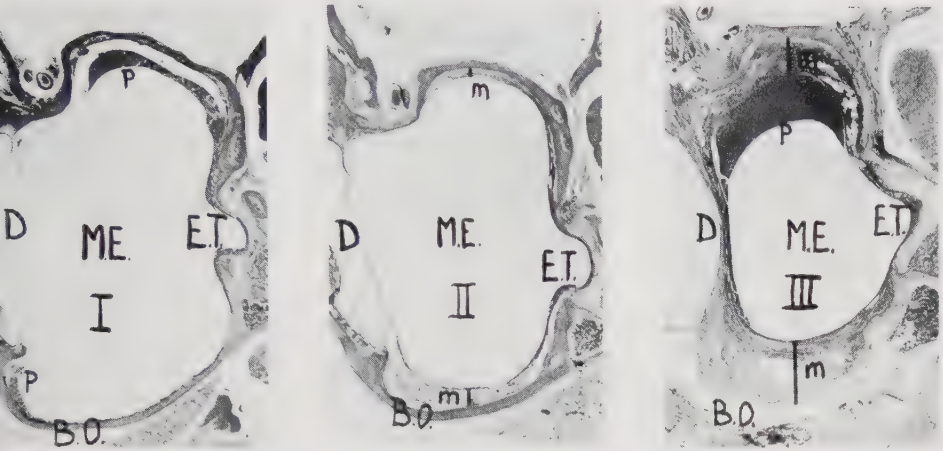


Fig. 16—18. Frontal section through middle ears in rats. M.E. = tympanic cavity. D = tympanic membrane. B.O. = bulla ossea. E.T. = tympanic orifice of pharyngotympanic tube. P = pus. m shows where the thickness of the mucous membrane was measured for the statistical analysis. I control animal. II animal given oxygen at flights in low pressure chamber and III animal not given oxygen. I discloses a purulent otitis, though with a very moderate mucosal thickness, II moderate mucosal thickness though, in this particular section, no pus, III strongly marked changes with pronounced thickening of the mucous membrane and tympanic membrane and a wholly purulent exudate.

Fig. 19. Frontal section through the nose in a control rat. Sep = nasal septum. Pus indicates a typical nasal inflammation between the conchae on the right side. Section from the same animal as middle ear I above (Fig. 16).

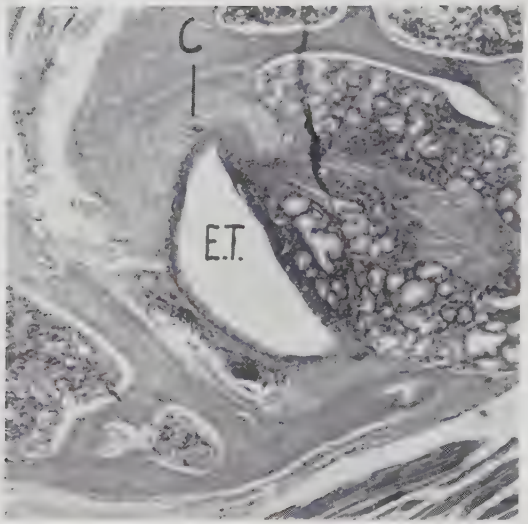


Fig. 20. Frontal oblique section through the pharyngotympanic tube in albino rat. E.T. = the tubal lumen itself, C. = tubal cartilage. No real streaks of muscles proceed towards the tubal wall.

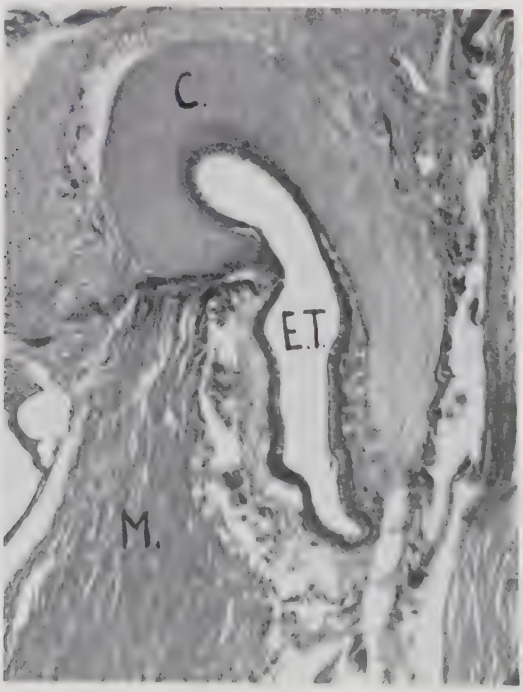


Fig. 21. Frontal oblique section through middle part of the pharyngotympanic tube in rabbit. C. = tubal cartilage. E.T. = tubal lumen. M. = musculus tensor veli palatini.

the pharyngotympanic tube.

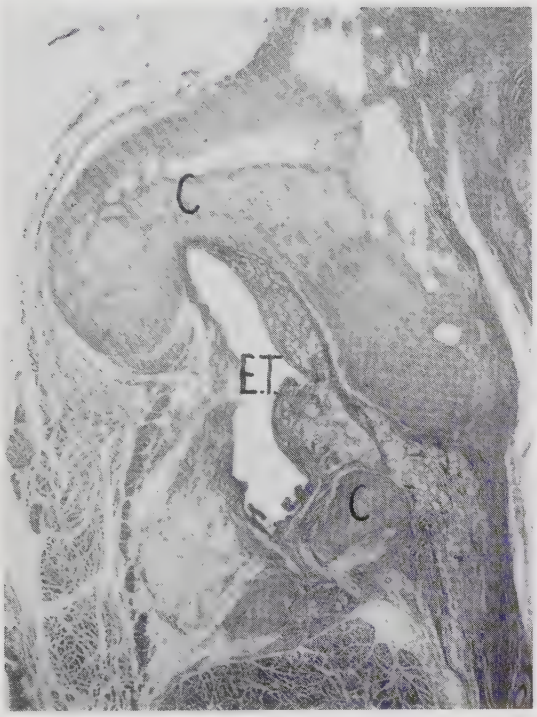
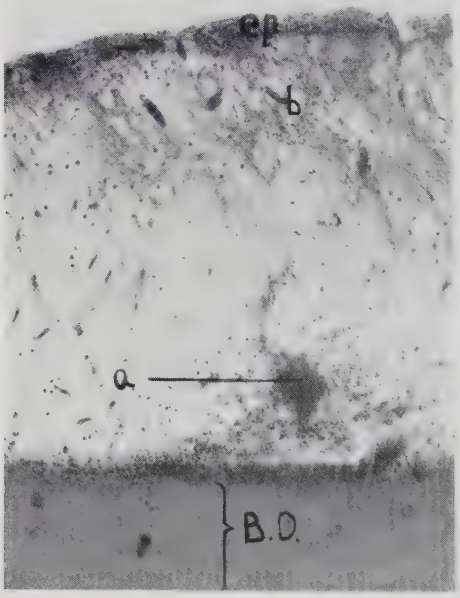


Fig. 22. Frontal oblique section through the middle part of the pharyngotympanic tube in Man. Woman of 49 years of age. Apart from size, the similarity to the tube of rabbit is striking, while the dissimilarity with that of rat clearly appears. The division of the tubal cartilage into one main plate and several minor cartilage parts is a common anomaly in Man.

Micro-photos of ear preparations from rabbits.

a) Frontal section through the anterior part of cavum tympani with a considerably swollen mucous membrane (m).

b) Frontal section further backwards. E.E. = acoustic canal. M.E. = cavum tympani. I.E. = inner ear on a level with S (fenestra ovalis). Below E.E. in the acoustic canal a parasite. The mucosal swelling reveals a typical localization with its most pronounced changes on the inside of bulla ossea, while mucous membrane above promontory is almost normal. Ep = epitympanum with some exudation around the auditory ossicles.



c) Detail picture from a) with increased magnification. B.O. = bulla ossea. Ep. = epithelium bordering on the cavum tympani. In the mucosa and submucosa an intense edema and, perivascularly, red blood corpuscles, in a large proportion at a, somewhat less at b.

Fig. 23. Rabbit 303 R. Low pressure chamber test.

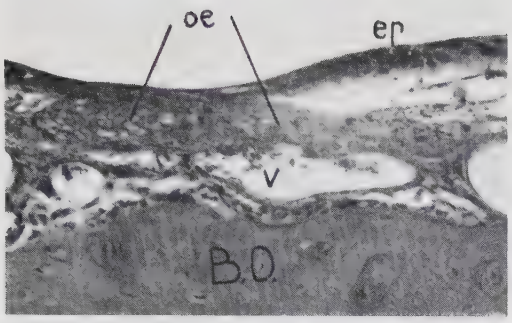


Fig. 24. Rabbit 302 R. Low pressure chamber test. This section illustrates the method of determining the quantitative changes, as described above, even though the mucosal patterns may disclose inconsiderable changes. OE shows the two different forms which the edema in the mucosa may present, viz., a vesicular structure to the right, and a more granular one to the left. ep shows the epithelium bordering on the cavum tympani and below it bleeding per diapedesis. V = dilated submucosal blood vessel.

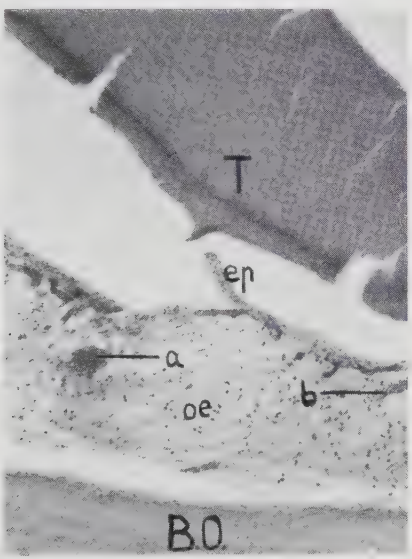


Fig. 25. Rabbit 307 R. Low pressure chamber test. In the cavum tympani in this particular specimen a granular, coagulated exudate (T), without cells, appears, while in other sections cells are found. ep = mucosal epithelium. In mucosa, a and b denote two vessels with red blood corpuscles perivascularly. OE indicates the edema, which, through the fixation, has assumed the same granular appearance as is most often noticed in the exudation.

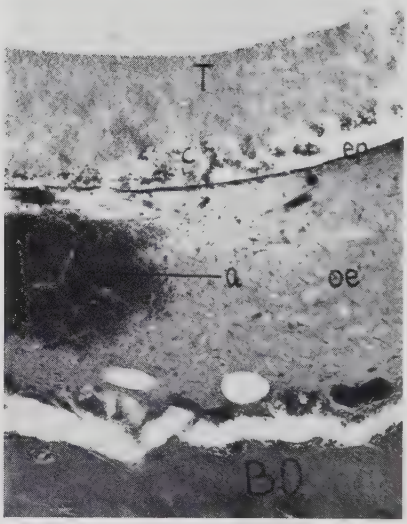


Fig. 26. Rabbit 309 R. Low pressure chamber test. T denotes exudate which has coagulated into a granular state. Against the mucous membrane lies a streak of lymphoid and mono-nuclear cells (c), mixed with one or two red blood corpuscles. a distinguishes a more massive formation per diapedesis, OE = the edema, in this instance particularly pronounced. The occurrence of vessels in a mucosal layer and in a deeper one in the submucosa towards the endosteum of bulla ossea (B.O.) is clearly discernible.

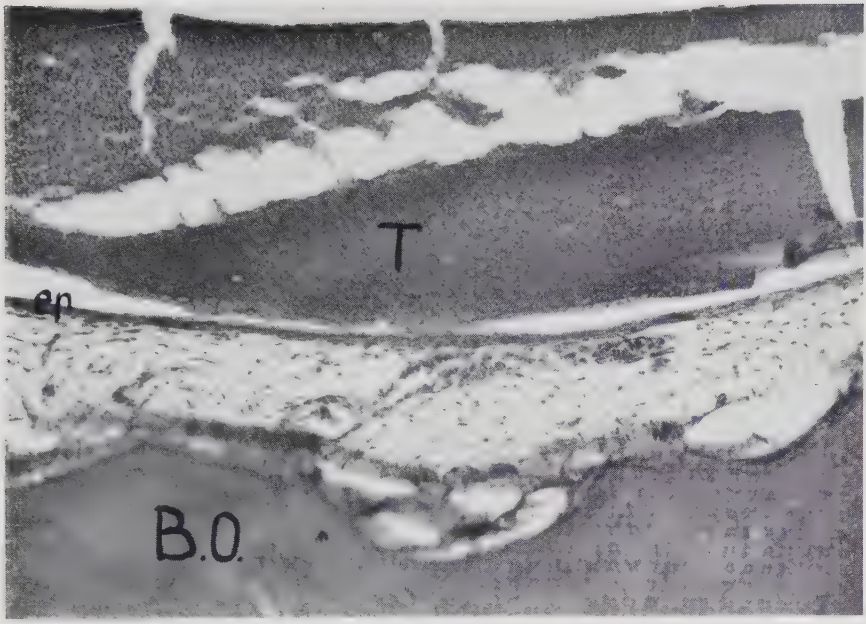


Fig. 27. Rabbit 318 L. Killed 4 days after the last ascent in low pressure chamber. B.O. = bulla ossea. Close to B.O. a pathologically thickened submucosa. ep = the epithelial delimitation towards cavum tympani, in which a granular, coagulated exudate without cells. In the mucosa in the middle part of the preparation a strongly dilated vessel with isolated red blood corpuscles extra-vascularly.

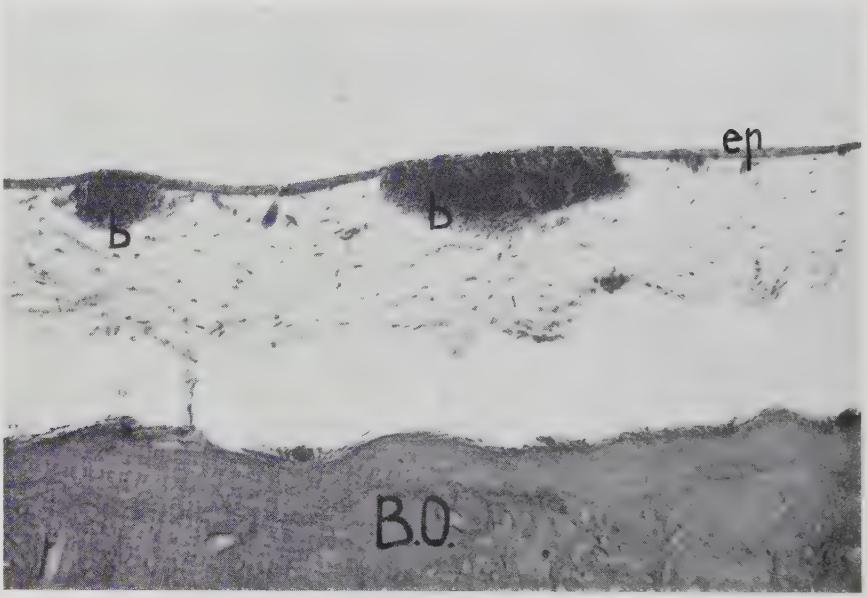


Fig. 28. Rabbit 321 L. Animal killed 10 days after the last ascent in low pressure chamber. At the histo-technical preparation the mucous membrane has loosened from bulla ossea (B.O.). Edematously swollen mucosa with two definitely limited bleedings (b) with a beginning destruction of the red blood corpuscles without any cellular reaction. ep = the epithelial delimitation towards cavum tympani.

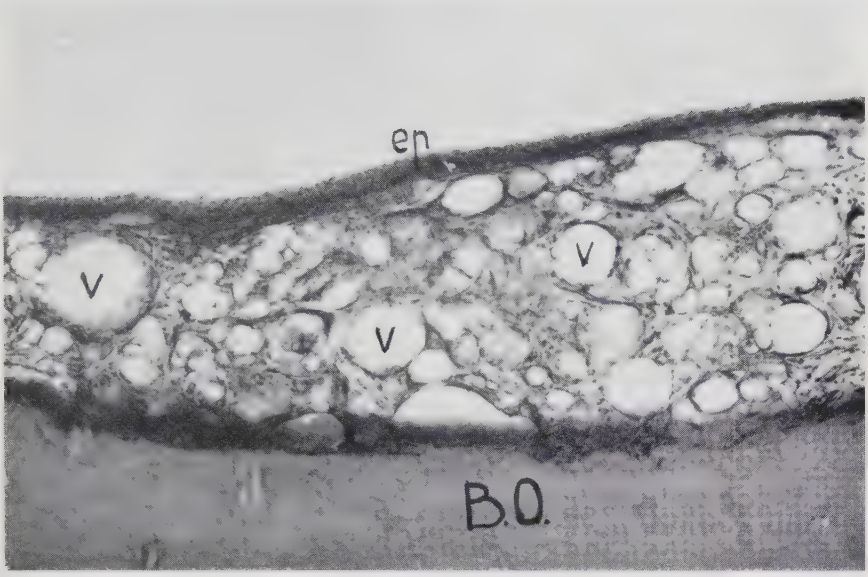
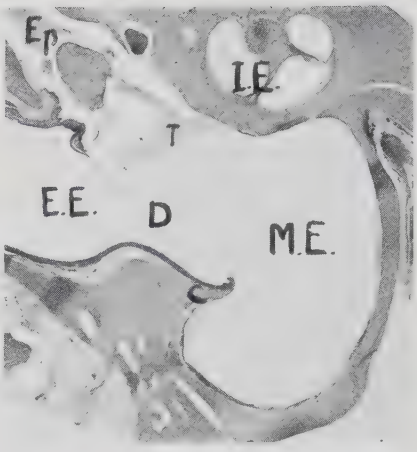


Fig. 29. Rabbit 326 R. Animal killed 15 days after the last ascent in low pressure chamber. In the mucosa a number of strongly dilated vessels (v), due to local stasis. These changes occur in several animals though less pronounced than here. B.O. = bulla ossea. ep = the epithelial delimitation towards cavum tympani.

30 a

30 b



31 a

31 b

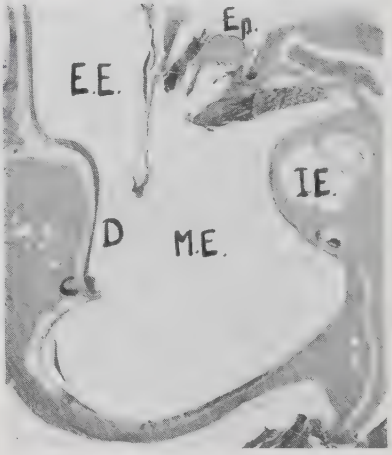
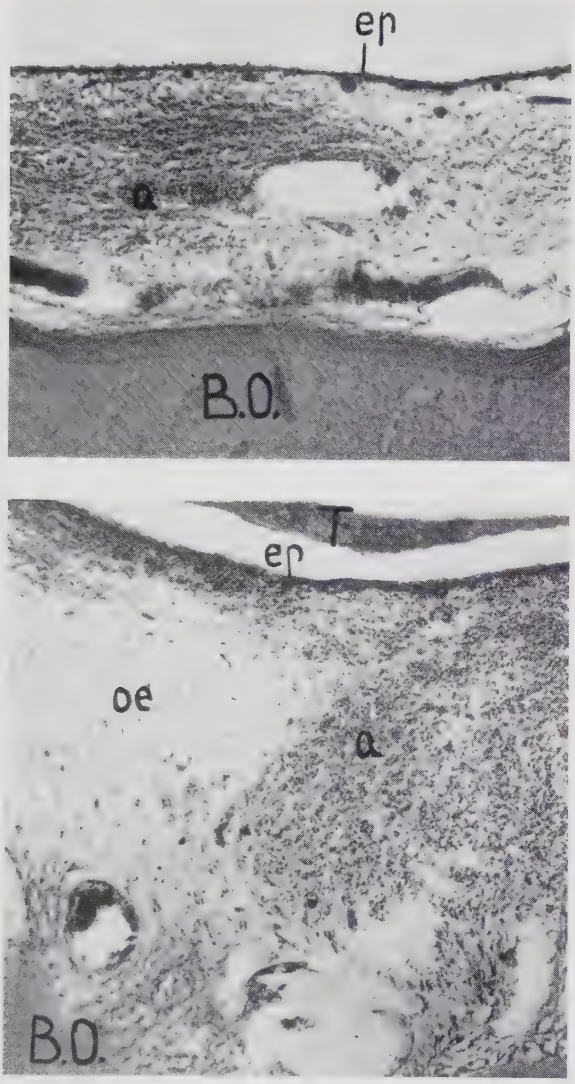


Fig. 30. Rabbit 356 R. Oxygen deficiency test.

a) Frontal section through anterior part of cavum tympani.
b) Section from the same ear through the posterior part of cavum tympani. The intense bleeding in the moderately swollen mucous membrane is conspicuous. Ep = epitympanum and around the auditory ossicles an exudate (T), free from cells.

Fig. 31. Rabbit 362 R. Oxygen deficiency test.

a) Frontal section through anterior part and
b) section through posterior part of cavum tympani. Mucosal swelling in both sections, strikingly pronounced as against the previous case. Exudate deficient in cells around auditory ossicles and at the crista (c) towards tympanic membrane.



30 c

31 c

Fig. 30 c (top picture) and fig. 31 c (below). Rabbits 356 R and 362 R. Details from preceding pictures showing edema, hyperemia and bleedings per diapedesis (a). The bleedings are strongly pronounced, hiding in extensive part of the mucosa and submucosa, all other structures. In spite of quantitative dissimilarities in mucosal reproductions and general aspects the histo-pathological pictures much resemble one another qualitatively.

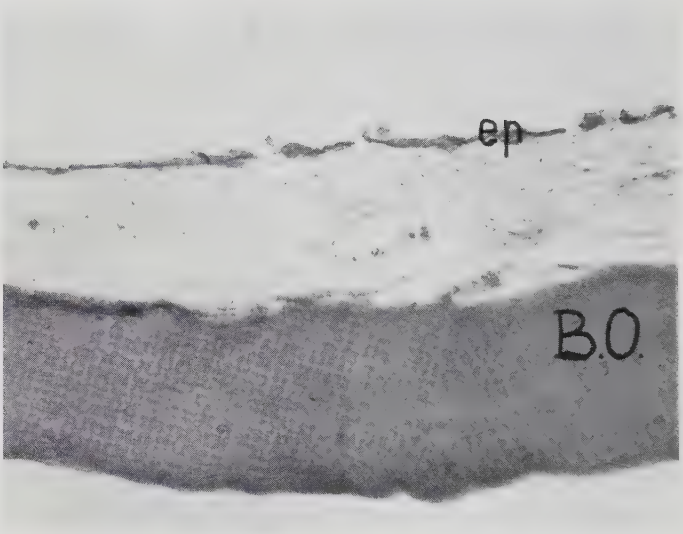


Fig. 32. Rabbit 353 L. Oxygen deficiency test. Detail picture of middle ear showing edematously swollen submucosa between the epithelium (ep) and bulla ossea (B.O.). No particularly conspicuous hyperemia. No bleedings.

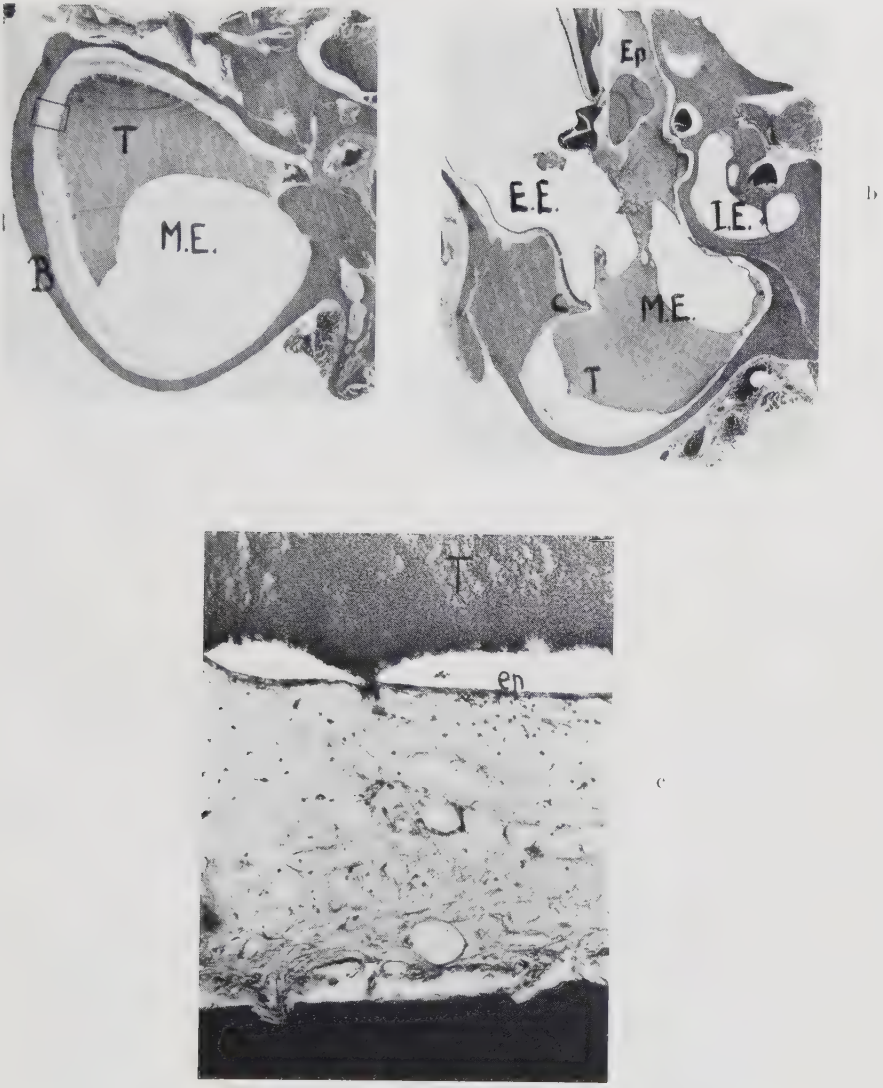


Fig. 33. Rabbit 411 R. Oxygen poisoning.

a) Frontal section through anterior part of middle ear.

b) Frontal section more backwards in the same ear. Mucosal swelling extremely conspicuous, as is also the exudation. The vesicular appearance of transudation below auditory ossicles is partly due to edema in the ligament of auditory ossicles.

c) Magnification of detail from preceding picture. The edema and faint monocytic cellular reaction are striking in the mucosa. The granular formation of exudation and the absence of cellular elements are also evident.

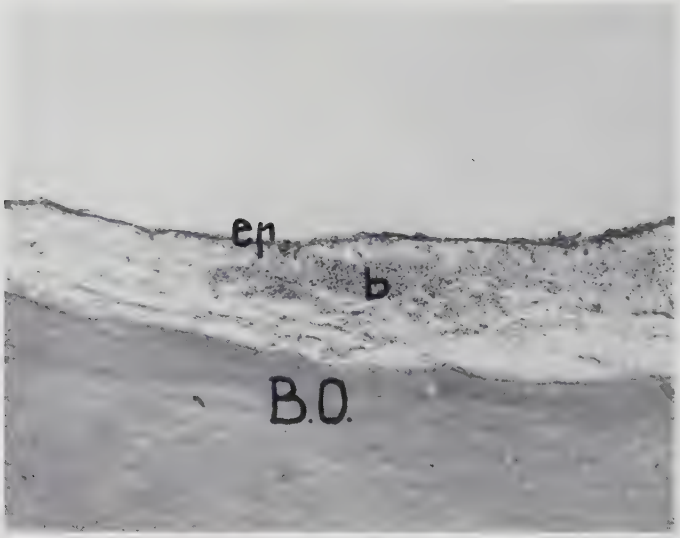


Fig. 34. Rabbit 406 L. Oxygen poisoning. Detail picture from middle ear disclosing a moderately swollen mucous membrane with a diffuse bleeding per diapedesis (b). ep = epithelium towards tympanic cavity. B.O. = bulla ossea.

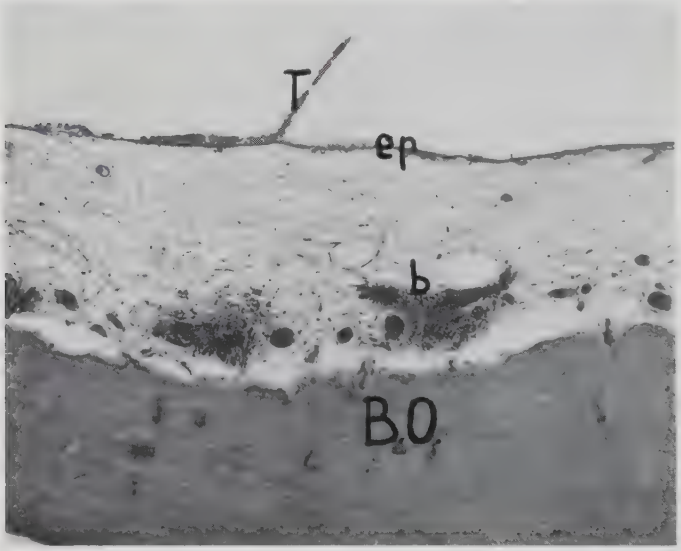


Fig. 35. Rabbit 412 L. Oxygen poisoning. Detail picture from middle ear showing a small exudation (T) in cavum tympani and, in the mucosa below the epithelium (ep), an edema. b = bleedings per diapedesis further down in the submucosa towards bulla ossea (B.O.).

Micro-photos of nose preparations from rabbits.

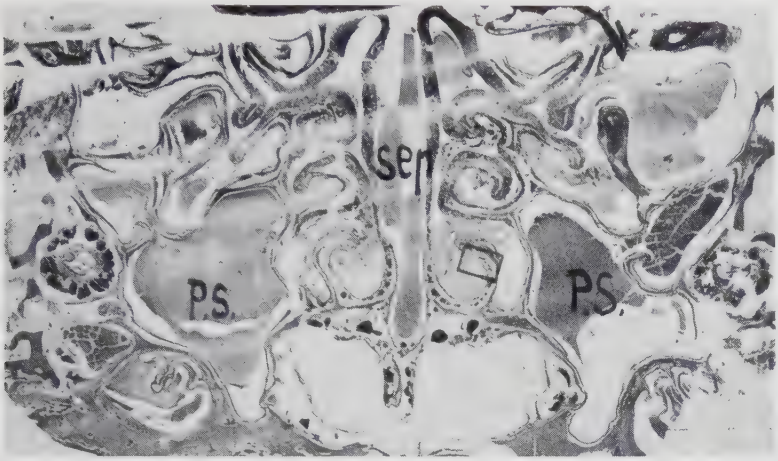


Fig. 36 a. Rabbit 306. Frontal section through the nose and paranasal sinuses in a rabbit, killed immediately after last flight in low pressure chamber. Histotechnical preparation not quite successful. Sep = nasal septum. P.S. = paranasal sinuses filled with a granular, coagulated exudation which is also to be found between the nasal conchae. As compared with the normal section the mucosal swelling especially of the conchae is noteworthy.

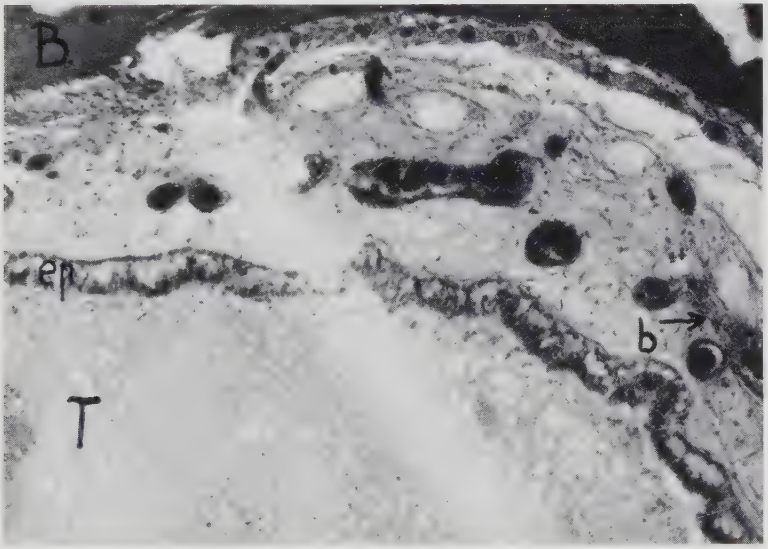


Fig. 36 b. Detail picture of the same animal, more magnified, reveals the typical changes. B = bone structure of the concha. T = the granular, coagulated exudate in the nasal duct, with isolated lymphatic and mono-nuclear cells. ep = the respiratory epithelium in the nasal mucous membrane. (b) indicates a perivascular bleeding per diapedesis in the submucosa. The latter is obviously edematous. An interstitial, granular, coagulated formation is evident everywhere submucously. No inflammatory reaction is noticeable. The submucous hyperemia is strongly pronounced.

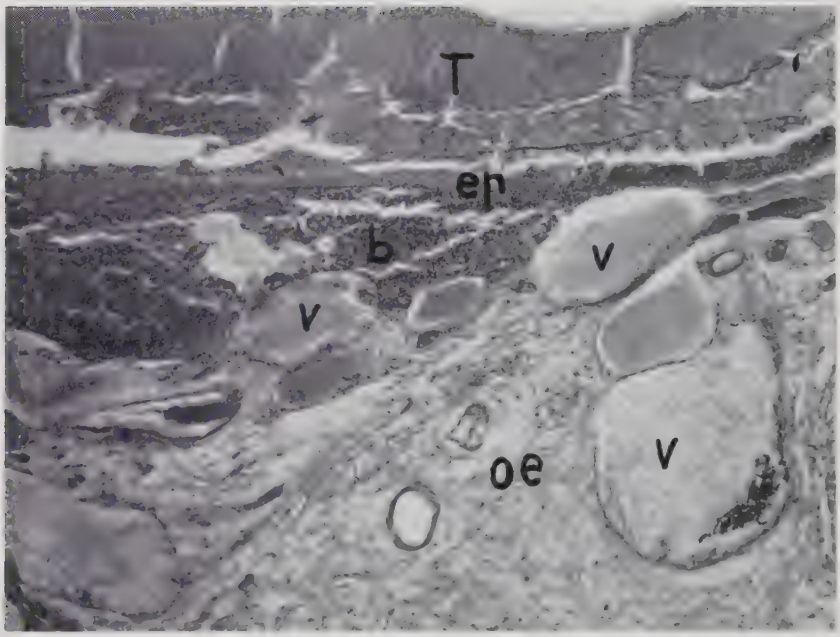


Fig. 37. Rabbit 362. Oxygen deficiency test. Detail picture. Shows nasal duct, in which a granular, coagulated exudate (T) without cells. ep = epithelium, below which to the left a bleeding (b). V = strongly dilated vessels, chiefly lymphatic ones. OE = edema in the submucosa.

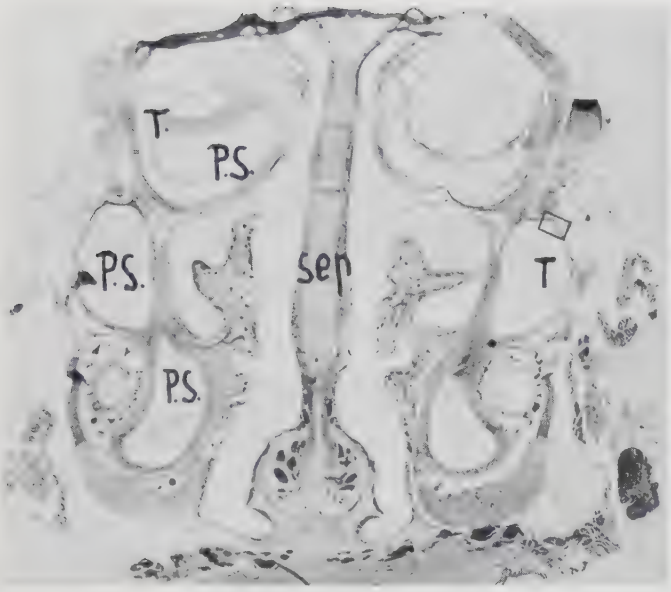


Fig. 38 a. Rabbit 411. Oxygen poisoning. Frontal section through anterior part of the nose and its accessory sinuses. In the general picture exudation visible both in the paranasal sinuses and the nasal ducts.

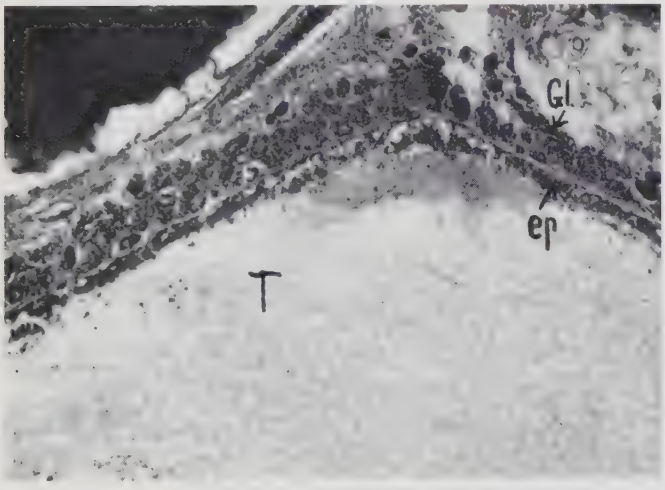


Fig. 38 b. Magnified detail from preceding picture. Hyperemia and slight edema in the sinusal mucous membrane with its profusion of glands. The granular formation of the exudate and the thinly scattered mononuclear cells are clearly discernible. Gl., glands of the mucosa.

Micro-photos of lung preparations.

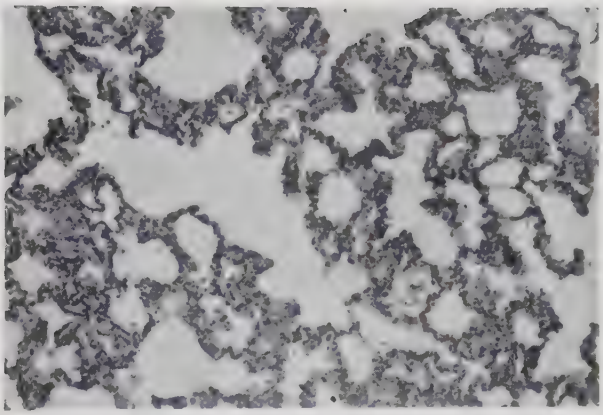


Fig. 39. Control animal (335).

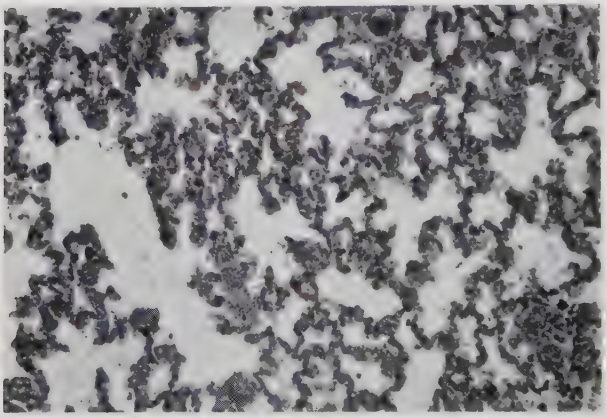


Fig. 40. Rabbit 302.

Low pressure chamber test. The capillaries in the alveolar wall are dilated and full of red blood corpuscles.

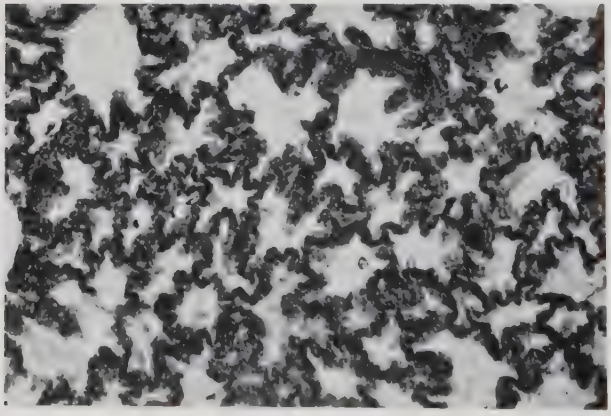


Fig. 41. Rabbit 308.

Low pressure chamber test. Shows the capillary hyperemia still more accentuated than in the preceding picture. In the alveoli is seen an edema, coagulated into granular clots.

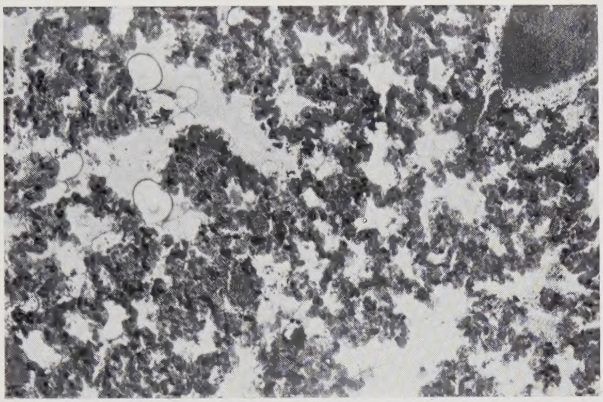


Fig. 42. Rabbit 356.

Oxygen deficiency test. An intense capillary hyperemia and in the upper left part of the preparation an alveolar edema. Some single interalveolar cells.

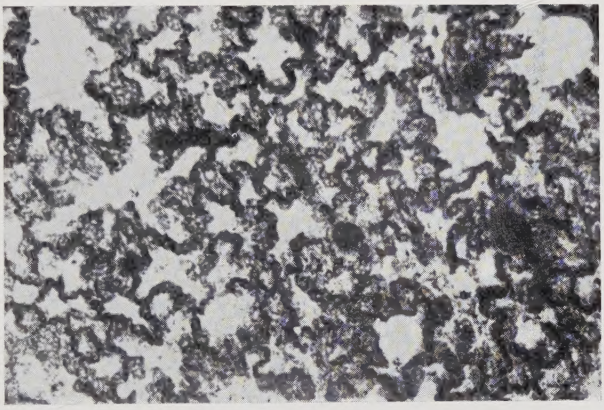


Fig. 43. Rabbit 363.

Oxygen deficiency test. Hyperemia as described before. An early stage of edema with isolated red blood corpuscles and monocytic cells in the alveoli.

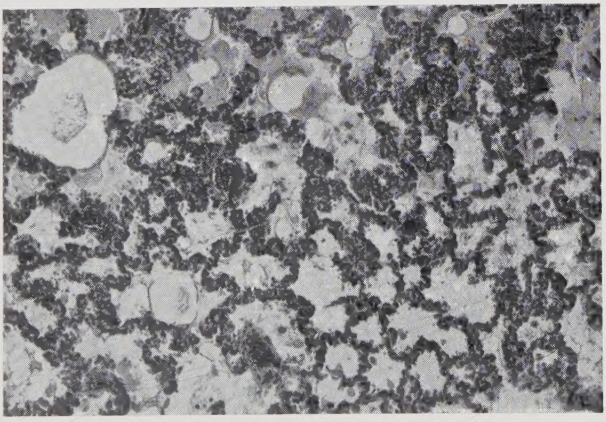


Fig. 44. Rabbit 406.

Oxygen poisoning. Intense capillary hyperemia. Alveolar edema with a small number of interalveolar red blood corpuscles and monocytic cells.

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